Neuromuscular Urgencies and Emergencies

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This book is dedicated to

Our patients, who taught us more than any book in the world!

Our students, who believe in us as their teacher and mentor!

Our families, mentors and friends!

Preface

Books cannot save lives but can aspire someone to do better. (Niraj Arora)

Neurology is an exciting field with new research constantly emanating to explain the amazing power of the human brain. Neuromuscular disorders as a subspecialty has emerged rapidly and is a constantly growing field. As clinicians, we deal with a significant proportion of acute events that could happen during inpatient or outpatient management. Given the constantly growing neuromuscular emergencies and time constraints in acute management, sometimes it becomes challenging for the treating neurologist to differentiate the disorders in a timely manner to deliver the best possible care. As more time is spent in front of computers instead of interacting with real patients, the support aspect of clinical neurology is losing its focus. The complexity of conditions as well as the detection rate of other neuromuscular conditions is rising.

With this focus in mind, the idea of writing a book containing neuromuscular emergencies was considered. The book is divided into ten chapters and deals with the important topics a neurologist or a treating physician might have to deal with in clinical practice. Each chapter starts with a brief introduction and explains the pathophysiology involved in disease along with symptoms, signs and management. The format of each chapter has been kept the same for easy grasp of the topic. The treating clinician can use this book as a handy reference instead of a sole textbook. The book has several easy-to-read flow charts and tables, which are essential in the time of emergency. Utmost care has been taken to verify the pharmacological doses of the medications that are currently being utilized for various treatments. However, there is always a possibility for a differing practice parameter at treating institutions. A significant focus of the book is the chapter on neuromuscular emergencies in the critical care unit. This chapter goes into extensive depth on all the acute neuromuscular pathologies that a clinician should be aware of. At the end of each chapter, an appendix and some important flowcharts have been added to give the reader some handy information while taking care of critically sick patients.

It is our hope that this book will serve as an essential aid for clinicians dealing with neuromuscular emergencies in clinical practice.

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Approach to Weakness

1

Sachin M. Bhagavan, Swathi Beladakere Ramaswamy, Tejas Mehta, and Raghav Govindarajan

Introduction

Approach to weakness is one of the most common neurological conditions that is encountered in clinical practice. It has a very broad differential, and multiple causes can be attributed to it. Therefore, it is important to understand the basics of weakness and adopt a systematic approach to encounter this clinical entity. This chapter deals with the basics of weakness and attempts to understand the motor pathway and clinical significance of lesion at each site. This would create a foundation on which different diseases could be easily understood and would help in accurate diagnosis of clinical conditions.

Approach to Weakness Based on UMN and LMN System

Weakness is loss of muscle strength, although the term is also used for generalized fatigue or functional limitations due to pain or limited joint motion, even though muscle strength is normal [1]. Therefore, evaluation of patients with weakness involves distinguishing true muscle weakness from lassitude or motor impairment not due to loss of muscle power, localizing the site of lesion within the neuromuscular system, and lastly, determining the cause of the lesion [1, 2].

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There are many ways to systematically approach the myriad lesions of the neuromuscular system causing true muscle weakness [3]. One such way would be to place the various lesions into categories determined by the organization of the neuromuscular system like, motor cortex and corticospinal tracts, anterior horn cells, spinal nerve roots, peripheral nerves, neuromuscular junctions, and finally muscles [3, 4]. The other most common approach would be to identify the pattern of weakness or distribution of weakness [3–5].

The constellation of motor pathways within the human central and peripheral nervous system involves two entities that guide voluntary movement: upper motor neurons (UMN) and lower motor neurons (LMN) [1, 2]. UMN constitutes pyramidal cells of the precentral gyrus (primary motor cortex) and projecting fibers that travel in several neural pathways (corticospinal tract, corticobulbar tract, colliculospinal tract, rubrospinal tract, vestibulospinal tract, reticulospinal tract) through the central nervous system (CNS) [1, 2]. LMN constitutes motor neurons (cell body) located in either the anterior grey column of spinal cord, anterior nerve roots (spinal lower motor neurons) or the cranial nerve nuclei of the brainstem and cranial nerves with motor function (cranial nerve lower motor neurons) [1, 2]. The nerves of the UMN pathway synapse with LMN pathway which transmits impulses to the neuromuscular junction (NMJ) to initiate muscle contraction. Figure 1.1 pictographically represents UMN and LMN system.

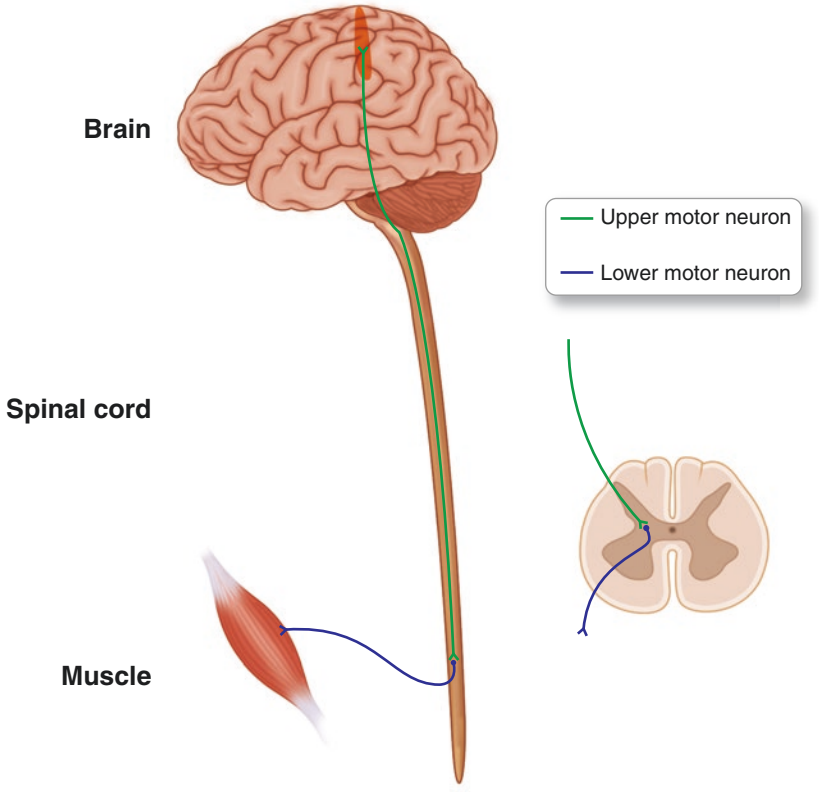

Fig. 1.1 Pictographic representation of UMN and LMN system

Table 1.1 Shows the physical exam findings correlating with location of lesion

UMN dysfunction	LMN dysfunction	NMJ dysfunction	Muscle dysfunction
Increased muscle tone (spasticity/rigidity) Increased muscle stretch reflex (hyperreflexia) Extensor plantar reflex (positive Babinski's sign)	Decreased muscle tone (flaccidity) Decreased muscle stretch reflex (hyporeflexia) Flexor plantar reflex (absent Babinski's sign)	Fluctuating weakness Worsening weakness with repeated activity (fatiguability) +/− Decreased muscle tone	Proximal muscles are most commonly involved +/− Decreased muscle tone

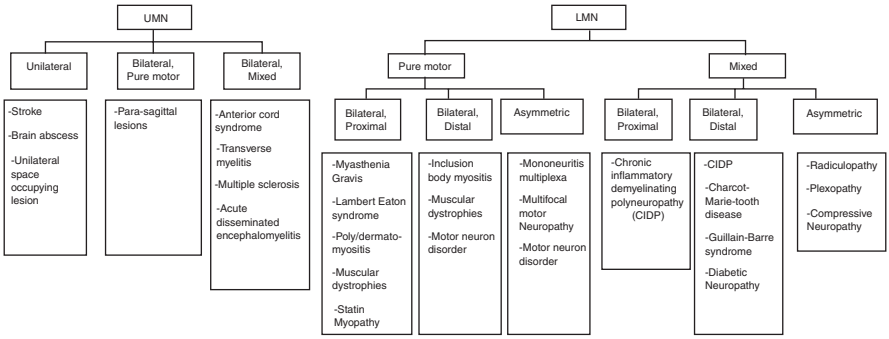

Fig. 1.2 Approach to weakness based on UMN and LMN signs

History and physical examination play a huge role in distinguishing and determining the location and cause of such weakness [3]. Table 1.1 describes the physical exam findings that correlate with location of lesions.

The following flowchart (Fig. 1.2) shows a basic outline on approach to weakness with the help of identifying UMN and LMN signs and a list of few examples in each category. Some diseases may have mixed UMN and LMN signs due to mixed central and peripheral lesion or UMN below the lesion and LMN at the level of lesion.

Approach to Weakness Based on Anatomical Localization

In neurology, accurate anatomical localization is the first step for reaching the diagnosis, and hence detailed examination is necessary to achieve so. As we know from above section weakness can be categorized into upper motor neuron (UMN) and lower motor neuron (LMN). Although categorizing weakness into UMN and LMN gives an important clue as to location of the weakness, it would not suffice to pin point the location. As mentioned, motor fibers traverse from cortex to the muscles, and lesions in different areas would be associated with different signs and symptoms. Assessing those signs would help for an accurate localization. This section

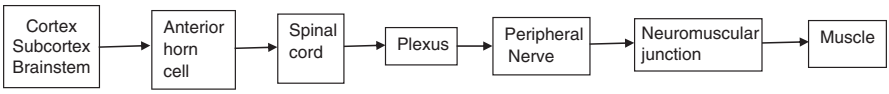

Fig. 1.3 Showing the pathway of corticospinal tracts

deals with other associated signs which favor the localization to particular anatomical area.

Pathways of most of the motor fibers are as shown in Fig. 1.3. This pathway is called corticospinal tracts or pyramidal tracts. Note that we describe only the corticospinal tract which is the most common pathway for motor fibers. Motor fibers also arise from other areas like cerebellum which are not described here as it is beyond the scope of this chapter.

Corticospinal tract is one of the most important descending tracts of CNS. It is divided into lateral corticospinal tracts (which forms 90% of fibers of corticospinal tracts) and anterior corticospinal tracts (forms 10% of fibers of corticospinal tracts). It originates at primary motor cortex present in the precentral gyrus. When an impulse is generated, it is conducted in the precentral gyrus (cortex) via the lateral corticospinal tracts through corona radiata, posterior limb of internal capsule (subcortex), cerebral peduncle, and basis pontis and decussates at caudal medulla (brainstem). Then it traverses contralaterally to anterior horn cell of spinal cord. Once the impulse reaches anterior horn cell, it is transmitted through spinal nerve root, plexus, peripheral nerve to neuromuscular junction where impulse is transmitted to muscle fibers, which leads to its contraction [6]. Any defect in the pathway will lead to weakness of the muscle. We will discuss lesion at each level in detail below.

Lesion at Cortex, Subcortex, and Brainstem

Weakness arising from cortex, subcortex, and brainstem predominately causes UMN type of weakness. History is important for determining if weakness was sudden or gradual. Sudden and maximal at onset should arouse suspicion for vascular causes like ischemic stroke and hemorrhagic stroke. Gradual and progressive weakness could be due to any space occupying lesion in brain like abscess and tumors. Along with corticospinal tract, corticobulbar fibers are also present, and hence cranial nerve involvement can also be seen. Most commonly seen are contralateral face involvement in the form of decreased sensation and facial weakness, although other cranial nerves (CN) can be involved. Weakness is typically UMN type, involving contralateral limbs as decussation occurs in caudal medulla.

Weakness in cortical and subcortical areas can be distinguished based on the pattern of weakness. Cortical weakness involves preferential areas of motor cortex due to the presence of motor homunculus. For example, involvement of face and arms is more than leg in middle cerebral artery stroke (MCA) compared to anterior cerebral artery stroke (ACA) which involves leg more than the arms and face. Subcortical

Table 1.2 Clinical features in a patient with lesion in cortex, subcortex, or brainstem [1, 8]

Structures	Associated symptoms/signs
Cortex	UMN type of weakness: contralateral involvement depends on affected cortical structure based on motor homunculus
	Contralateral sensory loss depends on affected cortical structures based on sensory homunculus
	Broca's aphasia
	Dysarthria
	Apraxia
	Hemineglect
	Behavioral abnormalities
	Impaired attention
	Motor impersistence
	Anosmia
	Paratonia
	Frontal release signs: grasp reflex, palmo-mental reflex, snout reflex
Subcortex	UMN type of weakness: involvement of contralateral face, arm, and leg to equal extent
	Contralateral sensory loss of face, arm, and leg to equal extent
	Dysarthria
	Impairment in movement and balance
Brainstem	UMN type of weakness: Contralateral limb (until caudal medulla) with ipsilateral facial involvement (at pons)
	Contralateral pain and temperature loss (medulla)
	Dysarthria
	Dysphagia
	Vertigo
	Ataxia
	Cranial nerve involvement depending on site of lesion

involvement like in posterior limb of internal capsule, corona radiata causes involvement of face, arm, and leg to equal extent because of the close proximity of the fibers. Similarly, sensory involvement is present based on the specific cortical area involvement on sensory homunculus, while subcortical involvement is typically more in extent due to close proximity of fibers [7].

In brainstem lesions, specific CN involvement can be seen like involvement of CN 3,4 in midbrain, CN 5,6,7,8 involvement in pons, and CN 9,10,11, 12 involvement in medulla. Associated signs are described in Table 1.2**.**

Lesion at Anterior Horn Cell

Anterior horn cells are present in the ventral aspect of spinal cord. These are cell bodies of motor neurons which terminate on striated muscles via ventral roots of spinal cord. It consists of cell bodies of the motor neurons which send axons to terminate on striated muscles via ventral roots of spinal cord. It is divided into medial and lateral group and further subdivided as shown in Fig. 1.4 [9]. Conditions that affect anterior horn cell are amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), West Nile encephalitis, and poliomyelitis.

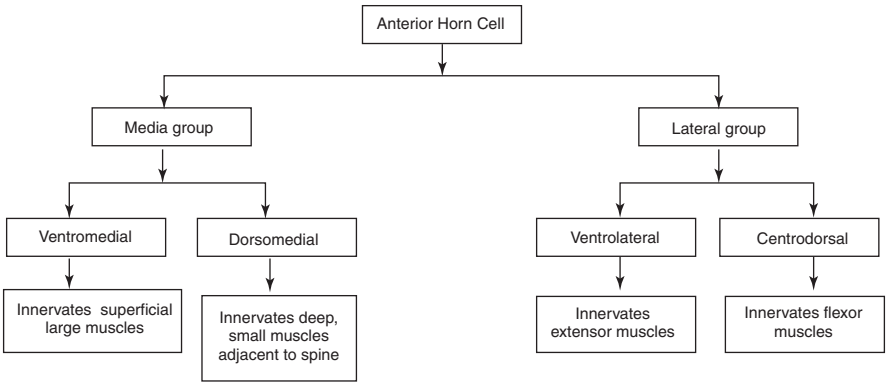

Fig. 1.4 Classification of anterior horn cell into groups and subgroups

Table 1.3 Clinical features in a patient with lesion in anterior horn cell

Weakness: UMN and LMN type in ALS affecting distal extremity
LMN type of weakness with symmetric proximal > distal muscle involvement in SMA
LMN type in West Nile encephalomyelitis affecting proximal > distal
Sensory is usually intact
Cervical UMN signs: Hofman sign and Tromner sign may be present in ALS
Thoracic and lumbosacral UMN signs: loss of superficial abdominal reflexes, extensor plantar response in ALS
Cognitive assessment for ALS
Bulbar signs: Snout reflex, pseudobulbar affect, exaggerated gag reflex, forced yawns
Impairment in consciousness in West Nile poliomyelitis
Bowel and bladder often involved in West Nile poliomyelitis and hence check rectal tone
Development of motor milestones may be impaired in SMA

Presentation is predominately motor in nature. Painless, progressive weakness is seen in ALS. It can be UMN or LMN type of weakness. Limb-onset ALS is the most common presentation starting in distal limb and spreads rostro-caudal [10]. Bulbar involvement is also seen [11]. Certain other features need to be evaluated as shown to arrive at an accurate diagnosis as shown in Table 1.3.

Lesion at Spinal Cord

Deficit due to involvement of spinal cord is called myelopathy. There are various causes of weakness arising due to myelopathy. Some of the causes are mentioned in Table 1.4.

Spinal cord extends from the foramen magnum where it continues with the medulla to the level of first or second lumbar vertebrae. It is divided into four regions: cervical, thoracic, lumbar, and sacral, each of which is composed of several segments containing motor and sensory nerves. To understand the signs and

Table 1.4 Different causes of myelopathy

Mechanism	Causes
Compressive	Tumors, spondylosis
Toxic	Botulinum toxicity
Inflammatory	Multiple sclerosis, neuromyelitis optica (NMO), myelin oligodendrocyte glycoprotein associated myelopathy (MOG)
Nutritional	Copper deficiency, Vitamin B12 deficiency

symptoms arising from spinal cord pathology, we need to know that there are ascending and descending tracts.

Main ascending tracts include antero-lateral spinothalamic tracts that transmit crude touch, pressure, pain, and temperature and posterior column that carries fine touch, joint position, vibration, and proprioception. First order neurons for spinothalamic tract ascend for 2–3 segments before crossing over and ascending up as anterolateral spinothalamic tract [12]. Therefore, any unilateral lesion of spinothalamic tract causes loss of crude touch, pressure, pain, and temperature on the opposite side 2–3 segments below the level of lesion. Whereas, second order neurons for posterior column (nucleus gracilis and cuneatus) decussate at medulla. Hence, spinal cord lesions can cause ipsilateral loss of fine touch, joint and proprioception and contralateral loss of pain and temperature which is a great localizing sign for spinal cord [12]. Main descending tracts include corticospinal tracts that help in voluntary movements. As we know they decussate at the caudal medulla, any lesion involving corticospinal tract at spinal cord produces contralateral hemiparesis.

Signs and symptoms depend on the level of spinal cord lesion. Cervical part of the cord gives spinal nerves that contribute to supply upper extremity, and lumbosacral region of the spinal cord supplies lower extremity. Pattern of weakness, sensory involvement, and reflexes can help determine the level of lesion. Generally, there is LMN type of weakness at the level of lesion and UMN type of lesion below the level of lesion. If weakness involves both upper and lower extremities (tetraplegia), then the level of lesion can be localized to cervical region. Similarly, weakness involving lower extremity with sparing of upper extremity would make thoraco-lumbar lesion a higher probability and cervical region less likely. Bowel and bladder incontinence should be kept in mind as it is affected in various spinal cord lesions. Pattern of reflexes also helps in localizing lesion. Sensory examination should be done in detail as decreased sensation to pin prick at dermatomal distribution could provide major clue to the level of lesion. Other aspects of sensory exam should also be conducted in much detail. Associated features are explained in Table 1.5.

Pattern of clinical signs and symptoms not only depends on the level of lesion but also on which area of spinal cord is involved. Since different tracts traverse the spinal cord at different regions, deficits can also help localize the area involved. Table 1.6 explains the different areas of spinal cord involvement and associated clinical features with it [13, 14].

Table 1.5 Clinical features in a patient with spinal cord lesion

Examination	Findings
Motor examination	Cervical involvement: Upper extremity (C5-T1) and/or tetraplegia Lumbosacral involvement: Lower extremity (T12-S4) and /or paraplegia
Tone	Decreased tone at level of lesion, may have increased tone below the level of lesion
Reflexes	Have decreased reflexes at level of lesion, may have increased reflexes below the level of lesion Examination of superficial reflexes: Corneal (CN V, CN VII) Palatal (CN IX, CN X) Scapular (C5-T1) Abdominal (T7-T12) Cremastric (L1/L2) Plantar (L5/S1) Anal (S3/S4) Deep tendon reflexes: Biceps (C5-C6) Triceps (C6, C7, C8) Brachioradialis (C5, C6) Patella (L2, L3, L4) Ankle (S1, S2)
Sensory	May have decreased sensation to pin prick at/or below the level of lesion May have decreased vibration/proprioception at/or below the level of lesion May have decreased temperature sensation at/or below level of lesion
Bowel and bladder	Urine retention/incontinence Priapism Rectal tone may be decreased in sacral injury
Other features	Tenderness of vertebrae
	Evaluation for pulmonary functions in case of cough, impaired breathing
	Lhermitte sign may be present
	Straight leg raise test may be present
	Autonomic features like miosis/mydriasis, anhidrosis/hyperhydrosis, orthostatic hypotension may be present

Lesion at Plexus

Any lesion at plexus affects a network of nerves and is called plexopathy. There are two main plexus that can contribute to weakness: brachial and lumbosacral plexus. Brachial plexus is formed by cervical nerve roots (C5-T1). Lumbosacral plexus is formed by nerve roots T12-S4. Focal plexopathy can produce unique clinical features. Table 1.7 explains the clinical features seen in plexopathy.

Lesion at Peripheral Nerve

Peripheral nerve lesions can be divided into myelinopathies (myelin involved) or axonopathies (axons involved). Major patterns are recognized based on the weakness being asymmetric or symmetric and involving proximal and/or distal muscles. This is because demyelinating polyneuropathy typically presents with both motor

Table 1.6 Clinical features of different areas of spinal cord involvement

Area of spinal cord	Affected tracts	Clinical features
Central cord syndrome	Bilateral central corticospinal tracts Lateral spinothalamic tract	Bilateral weakness, upper > lower extremities
Anterior cord syndrome	Corticospinal tract Spinothalamic tract	Complete motor paralysis Loss of pain and temperature below the level of lesion Light touch, vibration, proprioception spared
Posterior cord syndrome	Posterior column	Ipsilateral loss of vibration, proprioception, and fine touch below the level of lesion
Hemisection of cord (Brown-Sequard syndrome)	Ipsilateral posterior column Ipsilateral corticospinal tract Ipsilateral spinothalamic tract	Ipsilateral loss of vibration, proprioception, fine touch below the level of lesion Segmental flaccid paresis at level of lesion (LMN findings) while spastic paresis below the level of lesion (UMN findings) Contralateral pain and temperature sensation 2–3 segments below lesion
Complete transection	Involvement of all tracts bilaterally	
High cervical (up to C5)		Quadriplegia Anesthesia below level of injury Loss of function of phrenic nerve (C3, C4, C5) Urine and bowel retention initially followed by automatic reflex emptying after few days
Mid-lower cervical (C6-T1)		Sparing of shoulder (C5-C6), Involvement of elbow and wrist flexors (C6-C7), elbow and wrist extensors (C7-C8), and finger flexors (C8-T1) may be seen Involvement of bilateral lower extremity Anesthesia below the level of lesion LMN at level of lesion while UMN type below the lesion Horner syndrome may be seen Diaphragm is spared
Thoracic (T1-T12)		Paraplegia below T1 but spares upper extremity Abdominal reflex absent with lesions above T6 Upper abdomen reflex preserved with lesion at T10 while all abdominal reflexes present with lesion at level of T12 Anesthesia below level of lesion
Conus medullaris		Prominent bowel, bladder, and sexual dysfunction Signs more likely bilateral due to small area
Cauda equina (lumbosacral roots)		Lower extremity weakness depending on level of lesion Sensory loss with saddle anesthesia may be seen Bowel and bladder dysfunction may be seen

Table 1.7 Clinical features in a patient with lesion at level of plexus

Plexus	Causes	Clinical features
Brachial plexus involvement	Trauma, inflammation, pressure from tumors in the area, radiation therapy, during birth	Weakness of specific muscle/muscle group based on myotomal distribution Sensory disturbances present in multiple dermatomes Decreased or absent reflexes in that limb
Lumbosacral plexus involvement	Infection, neoplasm, trauma, radiation, hematoma, hip surgery [15].	Weakness involving hip flexors and adductors and/or knee extensors seen in lumbar plexus injury Foot drop/flail foot seen in upper sacral or lumbosacral injury [16] Sensory deficit involving anterior, medial thigh, and medial leg indicates lumbar plexus involvement Sensory deficit involving leg, dorsum of foot, posterior thigh, and perineum may indicate sacral/lumbosacral involvement

Table 1.8 Clinical features in a patient with level of lesion at peripheral nerve

	Conditions	Clinical features
Peripheral nerve	Myelinopathies: Guillain Barre syndrome/acute inflammatory demyelinating polyneuropathy (AIDP) Chronic inflammatory demyelinating polyneuropathy (CIDP) Hereditary sensory polyneuropathy Axonopathies: toxin, metabolic, infectious, immune mediated, vascular causes	Variable extent of weakness seen in distal and/or proximal muscles Sensory loss may or may not be present, if present, may involve multiple nerves and to a variable degree Autonomic signs may be present Deep tendon reflexes may be decreased or absent May or may not involve cranial nerve

and sensory symptoms with symmetric proximal and distal weakness while axonopathies present with symmetric distal upper and lower extremity weaknesses with sensory involvement [17]. Some examples of peripheral nerve disorders and general exam findings are discussed in Table 1.8.

Lesion at Neuromuscular Junction

Neuromuscular junction refers to a chemical synapse between a motor neuron and muscle fiber. This facilitates transmission of signal from a motor neuron to muscle fiber which leads to muscle contraction. Most common conditions associated are myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). Disorders of neuromuscular junctions have different signs and symptoms that need to be elicited. One of the most important clinical features that distinguish

Table 1.9 Clinical features in a patient with neuromuscular disorders [5]

	Examples	Associated features
Neuromuscular diseases	Myasthenia gravis Lambert-Eaton myasthenic syndrome (LEMS)	Usually have proximal muscle weakness, may have distal muscle weakness Fatigable weakness Extraocular symptoms very common Ptosis Bulbar symptoms can be seen Can involve respiratory muscles Usually no sensory abnormalities Presynaptic involvement: can have autonomic signs or post exercise increase in strength Postsynaptic involvement: fatiguability with post exercise

neuromuscular junction defects from other diseases is fluctuation of symptoms. Patients with MG typically present with fatiguability after repetitive activity, whereas patients with LEMS might have transient strength improvement after a brief exercise. Table 1.9 shows the main clinical features of patients with neuromuscular disorders.

Lesion at Muscle

Disease involving the muscle itself can cause weakness. There are numerous causes that could contribute to muscle diseases. Weakness is one of the main symptoms that patients usually present. Therefore, obtaining focused history involving onset, progression, painful or painless and pattern of weakness should be of utmost importance. Weakness could be proximal as seen in most myopathies or distal as seen in myotonic dystrophy. It can also involve bulbar muscles. Other symptoms like atrophy, stiffness, cramps, and myalgia can also be present. Table 1.10 explains the main features that can be seen in muscle diseases.

Approach During an Emergency

As mentioned in the topics above, there are several neuromuscular disorders which may involve the upper motor neuron, the lower motor neuron, or both. Although most of these conditions precipitate muscle weakness and are immediately noticed by the patient leading to an appointment with their primary care provider or a visit to the emergency department and eventually a neurologist leading to appropriate management of the condition, there are instances when the condition remains unattended, undiagnosed, or gets aggravated. In cases such as these along with a small fraction of cases which have been managed but yet worsen, the condition may take a turn for the worse and may lead to an immediate threat to the health and well-being of the patient.

Table 1.10 Clinical features in a patient with level of lesion at muscle [18]

	Few examples	Associated features
Muscle disorders	Myotonic dystrophy Inclusion body myopathy Dermatomyositis Duchenne muscular dystrophy Statin-induced myopathy	Limb weakness: van be proximal or distal depending on cause Muscle strength assessment in facial muscles, eyes, neck, spine, jaw Muscle bulk: wasting or hypertrophy Assessment for myokymia (continuous muscle activity) Muscle tone: may be normal, increased, or decreased Reflexes: decreased or normal deep tendon reflexes, superficial reflexes usually intact Gait assessment: Wide based gait in proximal muscle weakness; high steppage gait in anterior compartment of leg weakness Can have respiratory muscle involvement Possible cardiomyopathy Special signs: (a) Trapezius hump in fascioscapulohumeral dystrophy (b) Percussion and action myotonia: myotonic dystrophy (c) Gower sign: Duchenne muscular dystrophy (d) Winging of scapula (e) Gottron papules and heliotrope rash in dermatomyositis

These conditions evolve into emergencies and should be dealt with immediately to limit the morbidity and mortality associated with the condition. Most of these conditions lead to a disturbance in the supply of oxygen to the vital organs of the body including the brain. Although most of these conditions may lead to respiratory failure, there are some conditions which may have a detrimental effect on the other organ systems which may prove fatal as well. Table 1.11 summarizes the different signs and symptoms that imply respiratory failure. Table 1.12 mentions some conditions that may present with weakness as a feature and clues related to the disease process which may imply that it is an emergency.

Conclusion

Weakness is a very broad category of symptoms and needs detailed understanding for accurate diagnosis. This chapter highlights different approaches to weakness

Table 1.11 The warning signs of respiratory failure which should be monitored in patients with weakness

Warning signs for respiratory failure
Rapid, shallow breathing
Stridor
Use of accessory muscles
Single breath count less than 20
Inability to speak in complete sentences
Bulbar weakness
Orthopnea
Paradoxical abdominal motion

Table 1.12 The different clues associated with diseases which are indicators of emergency

Condition	Clues associated with diseases which are indicators of emergency
Stroke	Sudden and maximal weakness at the onset with features including but not limited to dysarthria, confusion, loss of pain and temperature, hemineglect, ataxia, and autonomic disturbances
Spinal cord infarction	Spinal cord infarction (SCI) like stroke presents with sudden and maximal onset weakness right from the start. The two types of SCI are described below [19] Anterior spinal artery infarct: Acute weakness Hypotonia with absent reflexes Total anesthesia below level of lesion Vibration and proprioception spared Posterior spinal artery infarct Mild and transient weakness Total anesthesia at the level of lesion Loss of proprioception and vibration below lesion
West Nile virus	Acute flaccid paralysis that may lead to respiratory failure [20]
Guillain Barre syndrome	Paralysis leading to respiratory failure with the following set of respiratory parameters: 1. Vital capacity (VC) less than 20 mL/kg 2. Maximal inspiratory pressure (MIP) less than30 cm H_2O 3. Maximal expiratory pressure (MEP) less than 40 cm H_2O 4. Reduction in VC, MIP, or MEP by more than 30% These parameters suggest imminent respiratory failure and are indications of mechanical intubation [21]
Myasthenia gravis	Bulbar dysfunction presenting as dysarthria, dysphagia, and impaired gag reflex typically seen in patients with high anti-MuSK antibodies Indications of intubation in these patients include [22]: 1. FVC less than 1 L 2. Negative inspiratory force less than 20 cm H_2Os 3. Declining tidal volumes
Lyme disease	Evidence of atrioventricular block on the electrocardiogram and features of meningitis [23, 24]
Hypokalemia	Cardiovascular manifestations evident on EKG as [25]: 1. ST depression 2. T wave inversion 3. Prominent U waves 4. Long QU interval

and helps to differentiate the pattern of weakness at different levels which is absolutely essential for diagnosis. It attempts to create a foundation which would make the subsequent chapters of neuromuscular emergencies easier to understand.

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Neuromuscular Respiratory Weakness

2

Jonathan F. Ang and Lakshmi Prasanna Digala

Introduction

The most common cause of death in neuromuscular diseases is chronic respiratory failure. The weakness of the diaphragm, intercostal muscles, and accessory respiratory muscles causes respiratory insufficiency and results in diminished ventilation [1, 2]. This type of insufficiency is known as type 2 respiratory failure or failure of the respiratory pump. It differs from type 1 hypoxic respiratory failure, which is secondary to the disease in the lung itself [2]. The main goal of management in these patients is to ensure adequate ventilation, mobilization of secretions, and prevention of pulmonary complications like infection and atelectasis [2].

Physiology

The normal process of breathing originates from the brainstem. The cortex can override these centers if voluntary breathing is desired. Medullary respiratory neurons in the pre-Botzinger complex bring about the rhythmic changes in the lung volumes resulting in breathing where several muscle groups are involved enabling changes in the lung volume. The following muscles are involved in the execution of standard work of breathing: [3].

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- Pharyngeal and laryngeal muscles – controls upper airway resistance.
- Diaphragm, external intercostal muscles, and neck muscles – enable inspiration.
- Expiration is normally a passive process.
- Rectus abdominis, external and internal oblique, and transversalis are the muscles of active expiration.

The diaphragm is the major inspiratory muscle innervated by phrenic motor nerve (C3–C5) [3, 4]. It constitutes Type 1 muscle fibers (45%), which maintain muscle tension for prolonged periods and are resistant to fatigue. The diaphragm has a considerable reserve to function, and unilateral phrenic nerve involvement has minimal effect on ventilatory capacity [3].

Unilateral diaphragmatic paralysis is often asymptomatic and may be discovered incidentally as an elevated hemi-diaphragm on radiography. These patients may develop dyspnea even with mild exertion, mainly if associated with intercostal muscle weakness or co-existing heart or lung disease. Fluoroscopy or ultrasound of the diaphragm helps detect the diaphragmatic paralysis [4].

Presentation

Neuromuscular weakness causing respiratory failure is usually nonspecific, chronic, and insidious in presentation [1]. Associated symptoms seen are tachypnea, tachycardia, orthopnea, accessory respiratory muscle use, ineffective cough, and weakness of neck and bulbar muscles.

Although the weakness of both inspiratory and expiratory muscle weakness causing respiratory pump failure is the primary mechanism behind the respiratory failure, muscle fibrosis or contractures could also contribute by limiting the chest movements and increasing work of breathing. Restrictive changes from coexisting chest wall deformities like kyphoscoliosis could be contributing to the limitation of chest expansion.

Reduced ventilation and ineffective cough from the weakness of respiratory, pharyngeal, and laryngeal muscles compromises the airway clearance and predisposes these patients to recurrent pneumonia and premature death [1, 5]. Additionally, bulbar muscular weakness may lead to ineffective swallowing that predisposes them to aspiration pneumonitis and pneumonia. Patients with bulbar dysfunction present with dysarthria, dysphagia, drooling, nasal speech, and tongue protrusion. Dysphagia may lead to malnutrition, dehydration, and aspiration pneumonia.

Patients with neuromuscular diseases with chronic respiratory failure usually present with the following clinical symptoms [1, 6, 7] (Fig. 2.1):

- Weak cough
- Orthopnea
- Hypersomnolence
- Sleep disordered breathing
- Headache upon waking up

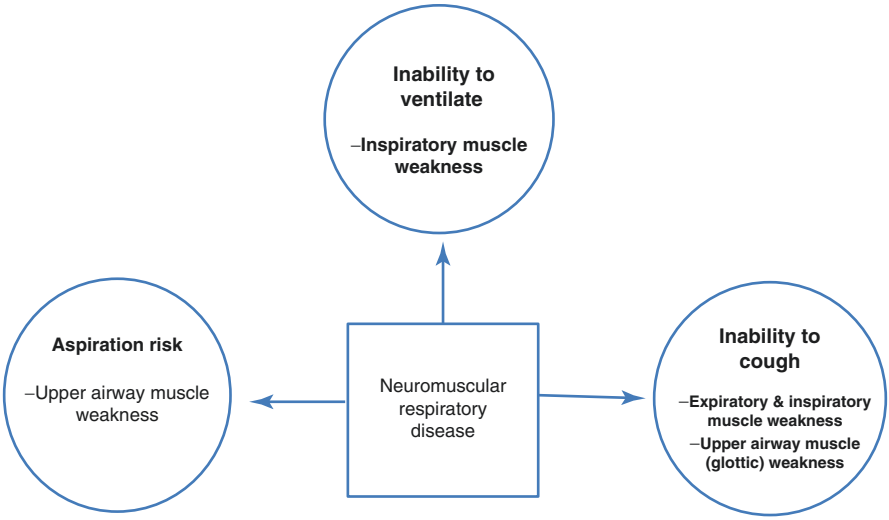

Fig. 2.1 Effects of NMD on the respiratory system

- Impaired concentration
- Fatigue
- Tachypnea, dysarthria, nasal speech

The symptoms are usually nonspecific and difficult to diagnose accurately. Respiratory failure in these patients is often underdiagnosed or falsely diagnosed as asthma, sleep apnea, or chronic obstructive pulmonary disease [1].

Assessment

Respiratory failure in these patients can be screened/diagnosed by the following tests [1, 7]:

1. Clinical encounter
   - Assess for bulbar muscle weakness – any history of drooling, change of voice, postprandial cough, and recurrent chest infections.
2. Sleep study
   - Often reveals sleep apnea or nocturnal hypoventilation. The presence of sleep-related hypoventilation is an indication for starting noninvasive ventilation. The scoring criteria for sleep-related hypoventilation in adults according to the current American Academy of Sleep Medicine are:
     – A PaCO2 of more than 55 mmHg for 10 min of sleep.
     – A rise of 10 mmHg of PaCO2 to a value more than 55 mmHg for 10 min of sleep [1].

- Sleep-related hypoxemia is diagnosed also by a sleep study and is diagnosed by the presence of a 5 min period of oxygen saturation of less than or equal to 88% [7]. The presence of sleep-related hypoxemia maybe an indication of respiratory muscle weakness.

3. Pulmonary function testing (PFT)
   - Used to confirm respiratory muscle weakness by a myriad of abnormalities on pulmonary function testing:
     - Restrictive pattern: normal FEV1/FVC ratio (more than 70% of predicted), reduced FEV1 (less than 80% of predicted), reduced FVC (less than 80% of predicted); confirmed by reduced TLC (less than 80% of predicted).
     - Decrease in the vital capacity ≥10% whilst recumbent compared to upright value.
     - Maximum voluntary ventilation (MVV) is reduced.
     - Maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP) is reduced.
     - Normal diffusing capacity of carbon monoxide in the absence of coexisting pulmonary parenchymal or vascular disease.
   - Assess effective cough
     - Peak cough flow of less than 160 L/min.
     - MEP less than 60 cmH2O.
   - The PFT is also used to assess the need for ventilatory support (discussed later).
4. Imaging with either chest radiography or chest CT reveals any coexisting scoliosis or parenchymal lung disease.

Although respiratory failure is toward the end of the disease course of neuromuscular diseases, early respiratory failure while the patient is still ambulatory is a distinct form seen in a few groups of diseases, which are shown in Tables 2.1 and 2.2.

Early recognition of the underlying diseases has potential implications on the management of the patient, especially prompt introduction of noninvasive ventilation, which is a highly effective treatment for symptomatic hypercapnia in patients with neuromuscular respiratory failure.

Table 2.1 Chronic neuromuscular diseases causing respiratory failure

Lower motor neuron/anteriorhorn cell disorder	Amyotrophic lateral sclerosis Toxic neuronopathy Distal spinal muscular atrophy type I
Neuromuscular junction disorder	Myasthenia gravis Lambert–Eaton myasthenic syndrome Congenital myasthenic syndromes

Table 2.2 Muscle disorders causing early respiratory failure

Metabolic myopathy	Myophosphorylase deficiency Adult-onset Pompe disease Mitochondrial myopathy Debrancher deficiency
Hereditary myopathy or muscular dystrophy	Myotonic dystrophy type I Myofibrillar myopathy Tropomyosin(TPM)3 myopathy Hereditary myopathy with early respiratory failure Oculopharyngodistal muscular dystrophy LGMD-limb girdle muscular dystrophies 2I, 2C-F
Acquired myopathy (autoimmune, inflammatory, toxic)	Inflammatory myopathy: dermatomyositis, polymyositis, inclusion body myositis Adult-onset nemaline myopathy Sarcoidosis (single case) Colchicine myopathy (single case) Multifocal motor neuropathy (single case)

Management

Noninvasive ventilation with airway clearance therapy is considered standard practice for patients with neuromuscular respiratory failure. The major goal of noninvasive ventilation is to ensure adequate ventilation. Evidence from randomized studies in ALS patients showed improvement in the quality of life and survival when treated with noninvasive ventilation (NIV) [1]. Criteria to recommend the introduction of non-invasive ventilation in these patients are:

- Sleep disordered breathing (criteria as discussed above).
- Assessment for the need of ventilatory support using PFTs:
  - Forced vital capacity is less than 50% of predicted.
  - Vital capacity of less than 15–20 ml/kg or less than 60% predicted, or having 1 liter of measured volume, or a drop of more than 30–50% from previous measurements.
  - MIP is less negative than −30 cmH2O.
  - MEP is below 40 cmH2O.
  - The "20-30-40 rule."

    Ventilatory support is initiated when the VC is less than 20 ml/kg, the MIP is less negative than −30 cmH2O, or the MEP is less than 40cmH2O.

The setting of NIV must target to ensure adequate minute ventilation. Adequate precautions like the second device with sufficient battery supply must be ensured in patients who use noninvasive ventilation during the daytime.

Some patients are able to tolerate NIV immediately, but others may need time to acclimate to the positive pressure to be fully comfortable with it. Ideally patients are introduced to NIV before its use becomes urgent, as this helps the patient get use to the positive pressure and improve compliance [8].

Mouthpiece Ventilation (Sip/Puff Ventilation)

Some patients need full-time ventilation and mouthpiece ventilation when awake [8]. An angled mouth-piece or straw-type mouthpiece is placed near the mouth so that patients can trigger a breath by creating a small negative pressure (sip ventilation). Mounting the ventilator on a wheelchair and suspending the mouthpiece on a gooseneck stand allows the patient to remain mobile and still have access to positive pressure as needed. Any mode of ventilation can be used. Limitations of this type of ventilation is that the patient must be able to create a good seal around the mouth piece to prevent significant air leak, access to the mouthpiece must always be assured by the caregiver, and the patient must have the ability to take a breath in deep enough to be able to create a small negative pressure to trigger the ventilator.

Although the patient's neuromuscular disease might not present with respiratory failure in the initial encounter, they are at high risk of developing one. Hence, prompt and timely screening is mandatory to identify patients that will benefit from NIV, as supportive respiratory therapies have proven to improve the quality of life when initiated promptly. Follow-up rate must be determined based on the established rate of progression of respiratory failure [7].

Tracheostomy

Out of all patients receiving mechanical ventilation, 10% of them undergo tracheostomy. [9] Early tracheostomy is when patients undergo the tracheostomy within 7 days of a hospital course. A meta-analysis involving 406 patients showed that early tracheostomy in patients with chronic neuromuscular diseases has no influence on the risk of pneumonia or mortality, although it did reduce the length of ICU stay and duration of artificial ventilation [9].

In ALS patients, the choice to undergo tracheostomy is 2–15% and are usually seen in younger patients that have family, higher education, and higher socioeconomic status.

Major factors influencing the decision to recommend the tracheostomy in patients with chronic neuromuscular disease are [9]:

- Severity of respiratory muscle involvement
- Rate of progression of the disease
- Presence of bulbar involvement.
- Ethical issues and cost
- Quality of life

Indications for tracheostomy in neuromuscular diseases are [9]:

- Excessive secretions
- Frequent pneumonia
- Peak cough flow of 160 L/min

– Progressive disease developing respiratory distress
– Orthopnea, daytime hypercapnia
– Coma or severely ill patients with bulbar weakness
– Failure or intolerance of noninvasive ventilation

Cough Assistance

Numerous respiratory therapies are available to support patients with neuromuscular diseases to help clear secretions. The diminished capacity to clear airway secretions is secondary to defective clearance rather than copious production [10]. Ineffective cough predisposes them to significant atelectasis, recurrent respiratory tract infections, and respiratory failure [1, 7, 11].

Peak cough flow is used to monitor the cough strength, and the value of less than 160 L/min is an indication to use cough assist devices.

Cough assistance includes manually-assisted coughing, mechanical insufflation-exsufflation, hyperinflation maneuvers, and secretion mobilization techniques like chest physiotherapy. Manually-assisted cough or quad cough is an abdominal thrust that a caregiver provides synchronized with the patient's voluntary cough effort. Mechanical insufflation-exsufflation is a device that delivers positive pressure breath, followed by negative pressure that sucks out immobilized secretions [1, 7].

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Rapidly Progressive Muscle Weakness

3

Tejas R. Mehta, Kunal Bhatia, and Niraj Arora

Anterior Horn Cells

Poliomyelitis

Poliomyelitis is caused by a single-stranded positive-sense RNA virus, which belongs to the group *Enterovirus C*. Poliovirus is transmitted from one person to another by oral contact with secretions or fecal material from an infected person. Most poliovirus infections cause asymptomatic viral replication in the gut. However, after an incubation period of 7–14 days, a subset of infected patients develops signs of minor illness which may include fever, headache, and sore throat [1].

Paralytic poliomyelitis, also called acute flaccid paralysis (AFP), occurs due to viral infection of the lower motor neurons (anterior horns cells) of spinal cord and brainstem. Neurological symptoms typically begin a few days after the onset of systemic signs. Central nervous system involvement presents as severe back and neck pain, aseptic meningitis, severe skeletal muscle weakness with or without bulbar muscle involvement, and in severe cases it may present as encephalomyeloradiculitis [1–3].

Symptoms and Signs

- Muscle weakness may vary from one muscle group to another. Muscle weakness worsens over the span of the first 72 hours and may affect bulbar muscles leading to dysarthria, dysphagia, and drooling.
- Involvement of respiratory muscles leads to respiratory failure which is often the cause of death.

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Table 3.1 A summary of findings that are seen during workup of a patient with polio and West Nile virus infection

Labs and tests	Polio	West Nile virus
CSF analysis	Polymorphonuclear leucocyte (PML) predominant leukocytosis which shifts to lymphocytosis over time Elevated protein level	Neutrophil predominant pleocytosis that shifts to lymphocytosis in later stages Elevated protein level
Serologic testing	Detection of poliovirus RNA in CSF by PCR	Detection of IgM antibodies in serum or CSF by the use of MAC-ELISA or PRNT is considered a gold standard for diagnosis
Electrodiagnostic test		
Sensory studies	Normal	Normal sensory nerve action potentials (SNAPs)
Motor studies	Slow conduction velocities with low to normal amplitudes	Nerve conduction velocities, fibrillatory potentials, and compound muscle action potentials (CMAPs) may be markedly decreased or normal reflecting the degree of paralysis
EMG findings	Decreased recruitment with fibrillation potentials, fasciculation potentials, and positive sharp waves in affected muscles	Decreased recruitment with fibrillation potentials, fasciculation potentials, and positive sharp waves in affected muscles
Imaging studies	No characteristic finding	MRI findings include meningeal involvement, intraspinal abnormalities including the spinal cord, nerve roots, and cauda equina

MAC-ELISA IgM antibody capture enzyme-linked immunosorbent assay, *PRNT* plaque reduction neutralization test

- Muscle tone is reduced and asymmetric with lower extremities being affected more than the upper extremities and slight predilection for proximal muscles more than the distal muscles.
- Hypo- or areflexia is a key feature of physical examination.

Table 3.1 denotes the laboratory and electrodiagnostic features of poliomyelitis virus-associated acute flaccid myelitis.

Management

There is no specific treatment for acute flaccid paralysis caused due to poliomyelitis. In general, treatment is supportive focusing on recognition of early signs of impending respiratory failure and bulbar dysfunction. Other supportive measures should include:

- Respiratory support including frequent bedside monitoring of respiratory function and pulmonary toileting.
- Physical therapy: Passive range of motion (PROM) exercises to prevent contractures.

– Splints: To relieve pain and spasms and prevent the development of deformities resulting from residual paralysis or weakness.
– Close monitoring in intensive care unit: Patients with bulbar movement require monitoring of blood pressure, heart rate, and autonomic dysfunction and immediate intervention with life support measures in acute deterioration. The use of plasmapheresis, immunosuppressive biologic modifiers, and IVIG (intravenous immunoglobulin) to treat patients with acute flaccid paralysis due to any cause has been discouraged by the Center for Disease Control although IVIG use has been studied for post-polio syndrome patients and is not recommended routinely [4].

  There are no treatments approved to reverse the anterior horn cell damage caused by the virus till date. Hence, preventive measures aimed at reducing the transmission of infection in the community should be a key strategy in reducing the burden of disease.

West Nile Virus (WNV) Infection

West Nile virus belongs to the family of arboviruses and is considered to be the most widespread of all other arbovirae. It is primarily transmitted by mosquitoes belonging to *Culex* species. After entering the human blood via injection by mosquito, the virus disseminates to visceral organs followed by invasion of the central nervous system. Neuro-invasion leads to formation of glial nodules with loss of neurons which is most pronounced in gray matter of medulla, midbrain, and pons.

Symptoms and Signs

Most cases with West Nile virus disease are asymptomatic. After an incubation period of 2–14 days, approximately 20–40% of patients affected may present with headache, back pain, muscle aches, anorexia, and fever. A maculopapular or roseolar rash may or may not be present in symptomatic cases. The rash lacks any specific pattern and does not help to differentiate from other infections. These acute symptoms last between 3 and 10 days and either resolve spontaneously or may progress to affect the nervous system. WN virus neuro-invasive disease presents as fever in conjunction with meningitis, encephalitis, or a mixed pattern of disease [5].

However, the most aggressive presentation of neuro-invasive WN virus disease is one that presents as acute flaccid paralysis resulting due to involvement of anterior horn cell similar to that seen in poliomyelitis. Patients present with asymmetric weakness of limbs that progresses rapidly within the first 2 days. Approximately 33% of the patients affected end up recovering their strength while the other 66% end up having deficits or fail to improve altogether. The most common cause of death in these patients is respiratory failure [6, 7]. A few patients with WN virus-associated neurologic disease may present with acute neuromuscular paralysis similar to Guillain-Barre syndrome due to immune-mediated destruction of the myelin sheath or axons [8, 9].

Table 3.1 denotes the laboratory and electrodiagnostic features of West Nile virus-associated acute flaccid myelitis.

Management

Although agents such as interferon, ribavirin, and immunoglobulins have been tested in animal models and small human studies, their efficacy in the treatment of WN virus infections still remains uncertain [10–12]. The treatment of WN virus infection is primarily supportive with focus on respiratory care and physical therapy [13–16]. Preventive measures are the cornerstone of controlling the spread of WN virus infection. These include mosquito control programs, personal protection measures, and screening of donor blood before transfusion.

Nerve

Guillain-Barre Syndrome (GBS)

GBS is an acute immune-mediated polyradiculoneuropathy which is characterized by rapidly evolving ascending weakness with decreased or absent deep tendon reflexes. The annual incidence ranges from 0.6 to 4.0/100,000 people per year. Males are affected more than females regardless of age, race, and ethnicities with increase in annual incidence with age [17, 18].

Pathogenesis

GBS is known to occur after various triggering events including surgeries, immunizations, trauma, infection, and bone marrow transplant out of which infection is considered to be the most prevalent. *Campylobacter jejuni* is the predominant antecedent infection associated with GBS and is seen in 25–50% of adult patients in Asian countries. Other infections that have been associated with development of GBS include HIV, Zika virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and influenza A. Systemic diseases such as Hodgkin's lymphoma, sarcoidosis, and systemic lupus erythematosus have also been associated with GBS [17].

One of the critical steps in GBS pathogenesis after antecedent infection is the generation of antibodies that cross-react with specific gangliosides located on peripheral nerves either at nodes of Ranvier or against antigens located on the myelin sheath. Exposure to infectious organisms leads to development of aberrant host immune response which cross-reacts with the antigens located on the peripheral nerves and spinal roots driven by molecular mimicry between microbial and axolemmal surface molecules. Destruction of peripheral nerve components by this mechanism leads to development of acute paralytic polyneuropathy [17].

In the acute inflammatory demyelinating polyneuropathy (AIDP) and the Miller-Fisher variants, the inflammatory response is directed against the myelin producing Schwann cells or myelin sheath. Endoneural and epineural infiltration by lymphocytes and monocytes are a characteristic pathologic finding which leads to segmental myelin degeneration. Whereas, the motor and motor-sensory variants are characterized by an immune response directed focally at the nodes of Ranvier which

leads to conduction block across the axon due to node lengthening, myelin detachment peripherally, dysfunction of the sodium channel, and an alteration of the water and ion homeostasis [18].

Symptoms and Signs

The cardinal features of GBS include:

- Progressive, symmetric muscle weakness with hypo- or areflexia. The weakness in AIDP commonly starts within the lower extremity and ascends to involve the proximal body although about a small subpopulation has reported the weakness to begin in the upper extremities or orofacial muscles [19, 20].
- Facial nerve palsy occurs in about 50% of the patients which may progress to oropharyngeal weakness. Oculomotor weakness occurs only in a small population of patients.
- Hypo/areflexia occurs in almost all patients with disease progression.
- Paresthesias in extremities are present in 80% of patients although they are mild in nature.
- Autonomic dysfunction is very common in GBS patients and may present commonly as diarrhea/constipation, hyponatremia, and bradycardia.

GBS progresses over a period of 2 weeks and after approximately 4 weeks of symptoms majority of the patients reach the nadir of the disease [19, 20].

Tables 3.2 and 3.3 denote the different subtypes of GBS and their characteristics.

Management

The mainstay of managing GBS is immunomodulation with plasma exchange or by the use of IVIg infusions [21, 22] (Fig. 3.1).

A short summary of the details of managing a patient with GBS is as follows:

Table 3.2 Summary of differences between clinical and other features of GBS subtypes

Variant	Clinical features	Antibody-directed against	Distinct feature
AIDP	Localized followed by widespread muscle weakness, cranial nerve deficits, and autonomic dysfunction	Antibodies directed against proteins P0, P2, PMP22	Accounts for about 90% of all GBS cases in Europe and United States
AMAN	No sensory involvement Areflexia Most rapidly progressive subtype Cranial nerves rarely affected	GM1a, GM1b, GD1a	More common in young Asians with a history of *Campylobacter jejuni* and predominantly occurs during summer as compared to other seasons
AMSAN	Both sensory and motor involvement	GM1, GD1a	Most severe form
Miller Fischer	Ocular involvement with ataxia and areflexia	GQ1b	Most common ocular manifestation is ophthalmoplegia

Table 3.3 A summary of uncommon and rare variants of Guillain-Barre syndrome

Variant	Characteristic features
Pure sensory GBS	GD1B antibodies targeting the sensory system leading to widespread sensory ataxia, areflexia, and mild motor involvement
Acute pandysautonomia	Autonomic dysfunction manifesting as dizziness, vomiting, pupillary abnormalities, fluctuating heart rate, orthostatic hypotension, abdominal pain, ileus, diarrhea, urinary retention and decreased sweating, lacrimation, and salivation. Decreased or absent reflexes with sensory symptoms may be present
Paraparesis	A relatively mild form of disease characterized by weakness limited to lower limbs during presentation although involvement of upper extremities may present in the later stages of the disease. Areflexia and electrodiagnostic abnormalities in the upper extremities may be present
Pharyngeal-cervical-brachial weakness	The antibodies are directed against GT1a, GQ1b, or GD1a leading to localized weakness of oropharyngeal, shoulder, and neck muscles with preservation of leg strength and reflexes
Acute bulbar palsy with ataxia, ophthalmoplegia, areflexia, and facial palsy	Considered as an overlap with Miller Fisher syndrome and pharyngeal-cervical-brachial variants of GBS. Limb weakness is absent in this form of disease

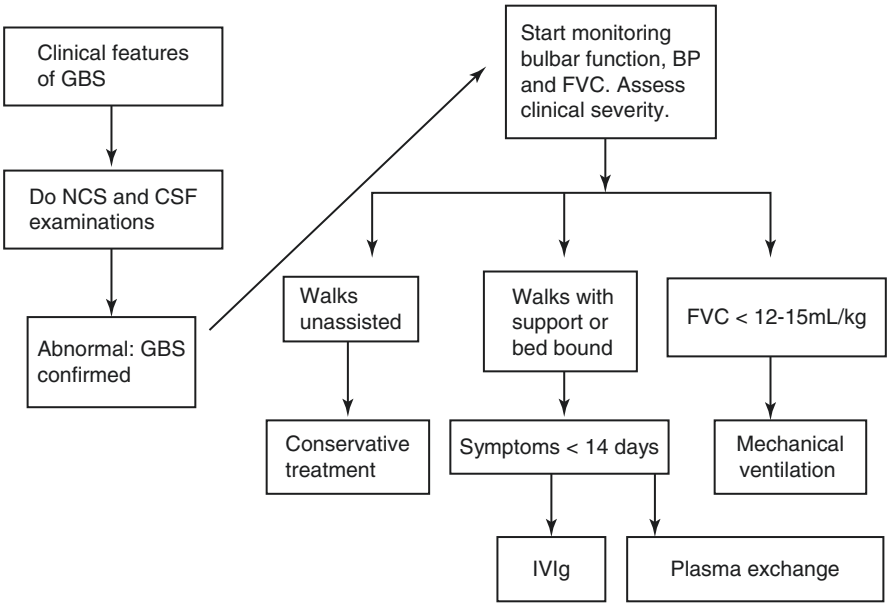

Fig. 3.1 Management strategy for cases suspected of GBS

– IVIg – A daily dose of 0.4 g/kg/day for a total of 5 days is recommended [20]. IgA deficiency and/or prior anaphylaxis reaction is not a contraindication to IVIG administration. In those cases, it is necessary to premedicate the patient and be able to manage the anaphylaxis with the medications in case the patient

develops a reaction to it. The incidence of serious reactions to IVIg in IgA-deficient patients was noted to be low in a large retrospective case series [23]. Patients with suspected IgA deficiency due to previous anaphylaxis reaction should have serum IgA levels and anti-IgA antibodies tested.

- Monitoring for aseptic meningitis, renal function tests, heart failure, and other thrombotic complications including stroke and myocardial infarction should be conducted while on therapy to prevent and manage complications.
- Plasma exchange – A total of five single plasma volume exchanges (40–50 ml/kg) are recommended with a continuous flow machine using albumin and saline as replacement fluids. Cardiac and hemodynamic parameters should be monitored regularly [24].
- In cases of no or poor response to IVIg or plasma exchange as measured on Hughes Disability scale, there is some role of rescue therapy with repeat dosing of IVIG or plasma exchange. The study noted improvement in disability scores at 1 month but no significant difference in length of stay in intensive care unit or disability scores at 3 and 6 months. It is important to note that rescue therapy was considered after a median period of 17 days (range 12–48 days) after the completion of primary treatment and patients who received IVIg as their primary treatment received IVIg during rescue treatment also. Clinical trials should be performed and should include only those patients who does not respond to initial treatment and should be randomized to treatment group or supportive group [25].
- Respiratory and cardiac monitoring is critical in all patients of GBS.
- Patients with autonomic dysfunction should undergo continuous EKG and blood pressure monitoring. Using antihypertensive medications in patients with blood pressure fluctuations should be done with extreme caution. Short-acting medications like labetalol, esmolol, and nitroprusside are generally preferred [26, 27].
- Airway protection should be offered in patients with bulbar weakness, excessive secretions, and respiratory insufficiency.
- Bedside pulmonary function tests including forced vital capacity (FVC) and negative inspiratory force (NIF) should be measured every 4–6 hours to monitor for early signs of impending respiratory failure. Parameters predicting the need for mechanical ventilation include rapid progression of disease, autonomic dysfunction, bifacial weakness, and bulbar dysfunction [28]. Respiratory parameters suggesting imminent respiratory failure and need for mechanical intubation include:
  (a) Vital capacity (VC) <20 ml/kg
  (b) Maximal inspiratory pressure (MIP) <−30 cm H2O
  (c) Maximal expiratory pressure <40 cm H2O
  (d) Reduction of more than 30% of VC, MIP or MEP
- FVC less than 12–15 ml/kg or NIF less than 25 cm H_2O are indications of intubation in patients.
- Chest physiotherapy, occupational therapy, and nutrition also play a vital role in management of these patients.

– Monitoring phosphorus levels is another important aspect to managing patients with respiratory issues since it has been reported to be a good prognostic factor to predict the need for ventilation [29].

Vasculitic Neuropathy

These are a heterogenous group of peripheral nerve disorders that arise due to systemic or non-systemic vasculitic disorders. The clinical presentation of vasculitic neuropathy depends entirely on the blood vessels involved and the severity of the disease process [30–47]. Inflammation of the walls of epineural and nutrient arteries due to autoimmune or underlying pathology is the main pathophysiological finding of vasculitic neuropathy [30, 37].

Symptoms and Signs

– Most patients develop both sensory and motor deficits, but 15% have predominantly sensory symptoms due to cutaneous nerve involvement [22].
– The symptoms associated with the presentation of vasculitic neuropathy depend entirely on the severity and the distribution of blood vessels that is involved.
– Organ-specific symptom along with neuropathy is a heralding feature. Pain and weakness are the predominant symptoms that evolve and progress over time.
– Small fiber neuropathies are only rarely vasculitic [48].
– Pure motor or autonomic presentations are uncommon [31].
– The most common presentation is a multifocal neuropathy or multiple mononeuropathy, produced by sequential ischemic insults to individual nerves. In other patients, individual mononeuropathies overlap, yielding an asymmetric polyneuropathy.
– Systemic vasculitic neuropathy (SVN) tends to be more severe than non-systemic vasculitic neuropathy (NSVN) [41, 48].
– Symptoms usually develop over weeks to months, with median delay from onset to diagnosis ranging from 2 to 8 months [32, 37, 39–41, 45, 48].
– The most frequently affected individual nerve is the common peroneal or peroneal division of the distal sciatic nerve [30, 32, 48].
– In the arms, the ulnar nerve proximal to the elbow is most commonly involved. Cranial neuropathies occur in only 10% of patients [32, 41, 48].

Table 3.4 summarizes the causes of systemic and non-systemic causes of vasculitic neuropathy.

Diagnosis

Table 3.5 denotes the laboratory investigations recommended in suspected cases of vasculitic neuropathy.

Management

– The first step in managing cases of vasculitic neuropathy is screening for possible triggers including but not limited to drugs, infections, or malignancies. If present, the trigger is resolved or eliminated which makes the condition of the patient significantly better.

Table 3.4 A summary of systemic and non-systemic causes of vasculitic neuropathy

Systemic (primary)	Systemic (secondary)	Non-systemic
Giant cell arteritis	Sarcoidosis	Non-systemic vasculitic neuropathy
Polyarteritis nodasa	Behcet's syndrome	Diabetic radicoplexus neuropathy (DRPLN)
Microscopic polyangiitis	Infections	Localized cutaneous or neuropathic vasculitis
Eosinophilic granulomatosis with polyangiitis	Drugs	
Granulomatosis with polyangiitis	Malignancy	
Essential mixed cryoglobulinemic	Inflammatory bowel disease	
Henoch-Schonlein purpura	Connective tissue diseases	

Table 3.5 A list of tests that are recommended in cases of suspected vasculitic neuropathy to ascertain the cause

Laboratory investigations for suspected vasculitic neuropathy
Complete blood count
Erythrocyte sedimentation rate (ESR)
C reactive protein (CRP)
Fasting glucose (2 consecutive days)
Electrolyte levels
Renal function tests
Liver function tests
Creatinine kinase
Serum protein immune fixation
Thyroid function tests
Hepatitis B and C serology

- The short-term goal in managing such patients is to stabilize the preexisting deficits and prevent the progression of these deficits.
- The management of a patient with vasculitic neuropathy depends on the progression of the disease. If the progression of the disease is rapid, i.e., if a new deficit is seen within 4 weeks of presentation, prednisone 1.0 mg/kg/day for 1-month along with cyclophosphamide, azathioprine, or methotrexate is used. A slow taper of prednisone to 10 mg/day at 6 months is then started. If the progression still continues, considering other therapeutic options such as rituximab and intravenous immunoglobulin is recommended. In case of no progression, remission maintenance with replacing cyclophosphamide with azathioprine or methotrexate at 3–6 months with reduction of prednisone to 5–7.5 mg daily after 6 months or stopping it should be considered and continued for at least 18–24 months [31].
- However, if the progression of the disease is not rapid, i.e., no new deficits are seen within the first 4 weeks of presentation, prednisone monotherapy with a dose of 1.0 mg/kg/day for 1 month followed by slow taper to 10 mg/day at 6 months is advised. In case of continued progression, combination therapy as mentioned above is considered. If no progression is seen in these cases, remission maintenance therapy of prednisone 5–7.5 mg daily is administered and is continued for 18–24 months [31].

Figure 3.2 summarizes the strategies of managing a case of non-systemic vasculitic neuropathy and neuropathy-predominant vasculitic neuropathy.

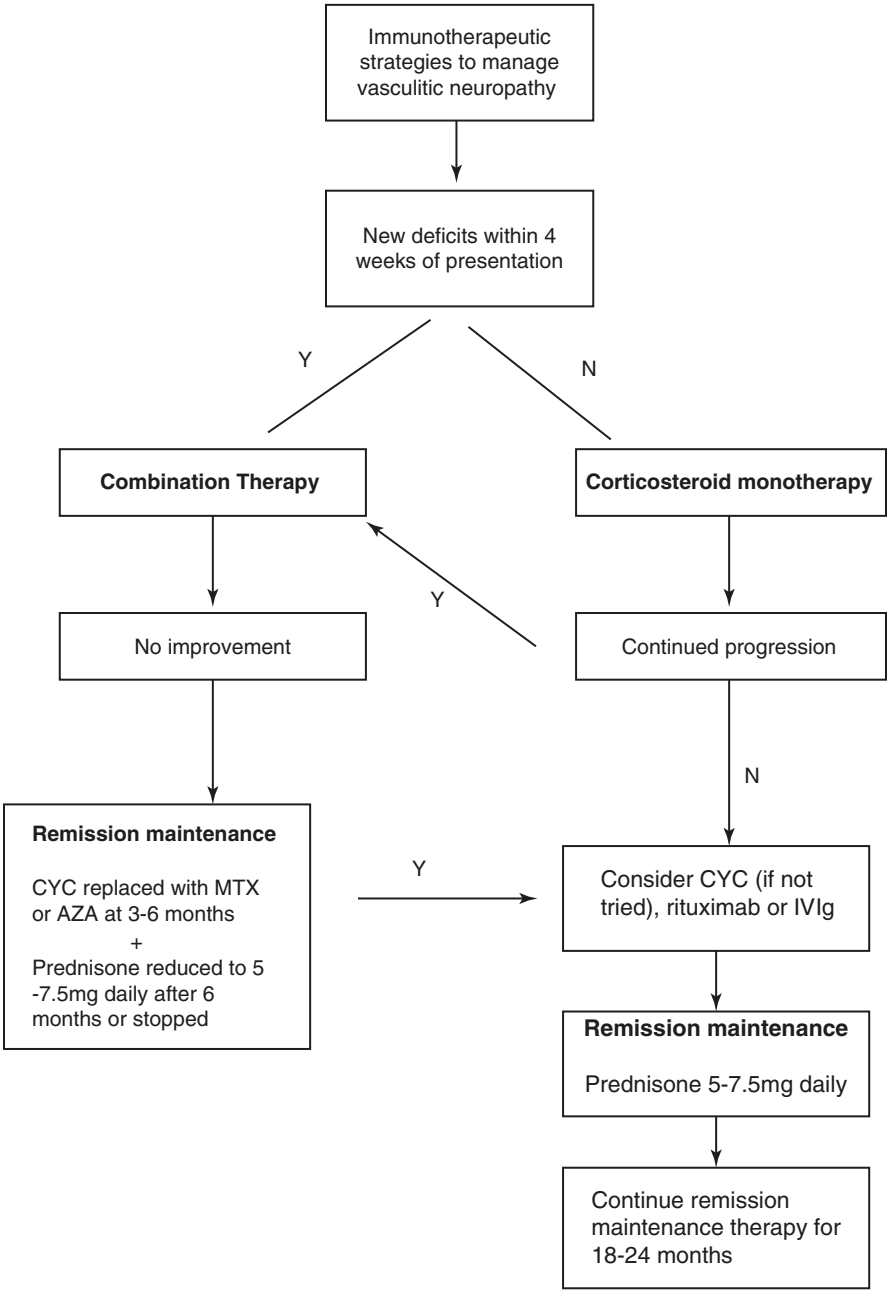

Fig. 3.2 Management strategy in NSVN and neuropathy predominant systemic vasculitis

Neuromuscular Junction

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a rare presynaptic disorder of neuromuscular transmission which manifests as proximal muscle weakness. The initial presentation can mimic that of myasthenia gravis, but progression of symptoms along with post-tetanic facilitation helps differentiating the two diseases.

Pathology

The mechanism behind the occurrence of LEMS is decreased acetylcholine (ACh) from the presynaptic nerve terminal due to destruction of voltage-gated calcium channels (VGCC) by autoantibodies that arise commonly due to an underlying malignancy. The most common malignancy that is associated with LEMS is small cell lung cancer [49, 50]. Other malignancies that have been known to be associated with LEMS include but are not limited to non-small cell lung cancer, lung adenocarcinoma, ovarian cancer, transitional cell cancer of urinary bladder, prostatic adenocarcinoma, and thymic neuroendocrine carcinoma [51–56].

Clinical Signs and Symptoms

- Slowly progressive muscle weakness more common in the lower extremity than the upper extremity without significant muscle atrophy is the common presentation.
- Hypo- or areflexia.
- Pathognomonic feature of LEMS is improvement in muscle strength and reflexes after repetitive muscle activity. This is referred to as post-exercise or post-activation facilitation and occurs due to an accumulation of calcium eventually leading to increase in ACh release in the synapse.
- Autonomic dysfunction including dry mouth, erectile dysfunction, and symmetric but sluggish pupillary light responses are common.
- Cranial nerve manifestations commonly presenting as ptosis and diplopia. An interesting sign includes paradoxical eyelid elevation after sustained upgaze in these patients [57].

Diagnosis

Electrodiagnostic studies and serological testing for VGCC antibodies forms the basis for confirmation of diagnosis.

Management

The first step in the management of LEMS includes evaluation for an underlying or occult malignancy.

- For patients with newly diagnosed LEMS and no known cancer, computed tomography of the chest, pelvis, and abdomen is recommended as a routine.
- MRI of the brain and spine should be conducted in cases where other neurological signs and symptoms are present.

– Testing for SOX antibodies in these patients is also considered helpful.

In patients with a negative initial evaluation, repeat testing should be conducted at 3 months for patients with DELTA-P (Dutch-English LEMS Tumor Association Prediction) score of more than 3, and 6 months for DELTA-P score less than 3.

The management strategy of LEMS depends on the severity of weakness.

– For patients with mild weakness and with no functional impact, regular monitoring of the patient's condition with no pharmacological therapy is recommended.
– For patients with moderate to severe weakness which affects their routine activity, amifampridine should be initiated. In cases where amifampridine isn't tolerated, guanidine can be used as an alternative [58–64].
– In patients with refractory weakness, IVIg is a good agent that is given 2 g/kg over a period of 2–5 days. Substitutes for IVIg include prednisone, azathioprine, mycophenolate, and cyclosporine [62].
– If a patient is refractory to other immunosuppressive agents, rituximab can be used [60, 61].

Myasthenia Gravis

Myasthenia gravis (MG) is an acquired autoimmune condition characterized by impaired neuromuscular junction transmission and is associated with antibodies against components of postsynaptic terminal [65]. This results in fatigable weakness of the appendicular, bulbar, and ocular muscles, which is the sole manifestation of the disease. The immune attack is commonly directed against antigens on the postsynaptic nicotinic acetylcholine receptor (AChR); however, other antigenic targets may also include muscle-specific tyrosine kinase receptor (MuSK) and lipoprotein receptor-related protein 4 (LRP4) receptor. A subset of patients with MG may develop a rapidly progressive weakness characterized by severe oropharyngeal and respiratory muscle weakness, termed as myasthenic crisis. As per the Myasthenia Gravis Foundation of America, myasthenic crisis represents a serious, life-threatening, rapid worsening of MG and potential airway compromise from ventilatory or bulbar dysfunction requiring intubation or noninvasive ventilation to avoid intubation [66].

Epidemiology

Epidemiological studies have shown the annual incidence of MG to range between 8 and 10 cases per 100,000 and a prevalence of 150–250 cases per 100,000 people [67]. The onset can be at any age and follows a bimodal distribution with a female predominance in the second-third decade and a male predominance in the sixth to eighth decade [68]. Myasthenic crisis can occur in approximately 10–60% of patients within the first year of their diagnosis and can be a presenting manifestation in up to 20% of MG patients [69]. In one hospital series which included patients with myasthenic crisis, the most important precipitating factor included documented infection in 38% of patients presenting with myasthenic crisis. The most common

infection reported was bacterial pneumonia followed by a bacterial or viral upper respiratory infection. Other common precipitants in order of prevalence included aspiration, changes in immunosuppressant dosing, corticosteroid initiation, medications, pregnancy, thymoma recurrence, and surgeries (during postoperative period) [68].

Pathophysiology

MG is an autoimmune condition characterized by disruption of neuromuscular transmission, resulting from direct attack against post-synaptic membrane proteins of neuromuscular junction, mainly acetylcholine receptors (AchR), by pathogenic antibodies. The autoantibodies produce T-cell-mediated attack through complement binding and activation, against the postsynaptic components of the neuromuscular membrane, causing accelerated degradation of these receptors by inducing conformational changes or by blocking acetylcholine binding. This results in a drop in the end plate potential causing abnormal or ineffective neuromuscular transmission, producing fatigable clinical weakness. Different pathogenic antibodies have been detected in the plasma of patients with MG. AChR antibodies are positive in up to 80–90% of patients with generalized MG. Up to 50% of patients with generalized MG, who are seronegative for Anti AchR, have antibodies against muscle-specific tyrosine kinase (MuSK) [70]. Lipoprotein-related protein 4 (LRP4) antibodies have been detected in 2–27% of patients with myasthenia gravis without AChR and MUSK antibodies [71, 72]. About 10–20% of patients with MG may have isolated ocular motor deficits for more than 2 years and do not progress to generalized MG, classified as "ocular MG." Nearly 50% of such patients have detectable AchR antibodies in serum [73]. Thymic follicular hyperplasia has also shown to contribute toward the pathophysiology of MG and is often present in patients with early onset generalized MG with onset <50 years of age [74, 75]. Whereas, thymic neoplasm or thymoma has been noted in 10–15% of all patients with MG, often characterized with generalized disease and having detectable AchR antibodies [76].

Symptoms and Signs

The hallmark of MG is fatigable weakness typically involving facial, ocular, pharyngeal, and proximal limb muscles [77]. Approximately 90% of patients with MG have oculo-bulbar weakness, but nearly one-third of patients may present with predominant proximal limb weakness without the presence of oculo-bulbar symptoms. Limb weakness is often symmetrical and can be precipitated by performing sustained muscle contraction or by repetitive muscle testing, a feature often utilized clinically to diagnose patients with MG. Ptosis, ophthalmoparesis, inability to sustain upgaze, head drop, jaw weakness, flaccid dysarthria, and a weak cough is commonly seen in patients with bulbar weakness. Another subset of MG patient may present with rapidly progressive weakness that is often preceded by a several days history of worsening limb weakness, diplopia, and/or bulbar symptoms such as dysarthria, dysphagia, weakness of neck extensors > neck flexors, and weak cough, leading to respiratory insufficiency. The voice is usually nasal in quality, indicating

pharyngeal weakness. Respiratory insufficiency can be often life threatening and is detected clinically by inability to complete full sentences, difficulty in counting aloud from 1 to 20 in a single breath, and paradoxical breathing pattern, collectively referred to as grave signs of neuromuscular respiratory failure signaling the need for ventilatory support. Myasthenic patients with muscle-specific receptor tyrosine kinase (MuSK) antibodies have rapidly progressive bulbar weakness at onset more frequently than myasthenic patients who are AChR antibody positive, and hence myasthenic crisis may be more common in MuSK antibody-positive individuals [78].

Patients with worsening weakness often take increased doses of anticholinesterase inhibitors (pyridostigmine) to alleviate their symptoms, which can precipitate myasthenic crisis with superimposed signs of cholinergic crisis. Signs and symptoms of cholinergic crisis may include: miosis, excessive bronchial secretions, salivation, sweating, bradycardia, abdominal cramping, diarrhea, and fasciculations. It is often difficult to differentiate between myasthenic crisis and cholinergic crisis, as a mixed picture is more common and is hence important for a clinician to recognize such symptoms [79].

Diagnosis

While the diagnosis of MG is primarily made clinically, supportive tests can confirm the diagnosis particularly in situations with less distinct clinical presentation. Some of the most common supplementary tests that can be performed include serology, acetylcholinesterase inhibitor (AChEI) test (edrophonium), and electrodiagnostic testing including repetitive nerve stimulation (RNS). Edrophonium test involves administration of a short-acting AChEI in a stepwise fashion and observation of clinical improvement. This test should always be carried out with frequent monitoring of heart rate and BP as it can cause possible bradycardia or asystole, requiring use of atropine. An ice pack test can also be used as an alternative in patients who are at increased risk of developing bradyarrhythmia after administration of edrophonium.

Findings on electrodiagnostic testing, including RNS and single fiber EMG, establish the diagnosis in most patients [80]. A characteristic electrophysiological response includes recording a decremental response on RNS, which is defined as >10% decrease in compound muscle action potential (CMAP), and has a sensitivity of 75–80% in generalized MG and 50% in ocular MG. Single fiber EMG, which includes recording potential from two muscle fibers stimulated simultaneously by one axon, is the most sensitive test for diagnosis of MG (sensitivity >95%). Increased jitter is observed on single fiber EMG in patients with generalized and ocular MG [81].

Testing of serum antibodies is readily available and is a simple and reliable diagnostic method available. Physicians should be aware that approximately 15% of patients with generalized MG and in up to 50% of patients with ocular forms of the disease may be seronegative on testing negative for AChR antibodies and MuSK antibodies [82].

Table 3.6 A list of tests that are used to diagnose MG

Bedside tests	Serology	Neurophysiological testing
Ice pack test Edrophonium test	Acetylcholine receptor (AChR) antibodies MuSK (muscle-specific tyrosine kinase) antibodies LRP4 (lipoprotein-related protein 4) antibodies Seronegative myasthenia Other antibodies antistriational antibodies, anti-titin, and anti-ryanodine)	Repetitive nerve stimulation Single fiber EMG (SFEMG)

A clinical classification has been developed and published by the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America to achieve a more uniform description of the different subgroups of patients affected by MG and their disease severity [83].

Table 3.6 denotes a list of tests that are used to diagnose MG.

Additional Diagnostic Testing

All patients with a new diagnosis of MG should be screened for thymoma by ordering CT chest with contrast [84]. In addition, patients should be screened for common community-acquired infections and metabolic derangements that could exacerbate the weakness causing myasthenic crisis. Simple bedside respiratory parameters, which may include serial measurement of forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), should be used to monitor progression of weakness in patients with bulbar weakness and/or weakness of head extensors/flexors.

Management

Management of patients with myasthenia gravis, particularly in patients with worsening or rapidly progressive weakness, begins with assessment of the degree of weakness, bulbar dysfunction, and respiratory compromise. Patients with myasthenic crisis often require ventilator support and constitute a neurological emergency. Performing an arterial blood gas analysis (ABG) can provide information related to the severity of respiratory failure and can guide selecting the preferred method of ventilatory support. Respiratory therapists should measure MIP and FVC as objective measures of respiratory muscle strength serially along with monitoring of cough and swallowing function. In patients without hypercapnia, prompt initiation of noninvasive ventilation with a bilevel positive airway pressure (BiPAP) can avert the need for intubation and has been shown to reduce the duration of ventilatory assistance by more than half. Even patients with severe bulbar weakness can tolerate noninvasive ventilation if they receive diligent respiratory care with frequent suctioning of oral and respiratory secretions. Based on retrospective studies, few parameters have been used in clinical practice to predict failure of noninvasive ventilation (NIV) in myasthenic crisis: severe hypercapnia ($PaCO_2$ >45 mm Hg), hypoxemia (PaO_2 <60 mm Hg), and serum bicarbonate concentration <30 mmol/L [85, 86]. Patients that progress to requiring intubation should be offered a

non-depolarizing blocking agent (e.g., rocuronium, vecuronium, cisatracurium) to prevent prolonged blockade that can exacerbate weakness in myasthenic patients [87]. Other supportive measures include use of bronchodilators to maintain airway patency, aggressive chest physiotherapy, regular suctioning, and bronchoscopy to promote airway clearance and use of cough assist devices. In addition, medications that can impair neuromuscular transmission and worsen weakness, such as beta-blockers and aminoglycosides, should be avoided. Table 3.7 shows the most common drugs, with the strongest evidence, that are known to precipitate or worsen weakness in MG patients [88–90].

The pharmacological treatment in patients with severe exacerbation or myasthenic crisis can be discussed under the category of symptomatic treatment with cholinesterase inhibitors and immunosuppressive therapies. Acetylcholinesterase inhibitors (AchEI), particularly pyridostigmine, is the preferred drug for symptomatic treatment in all forms of autoimmune MG. It is usually started at a dose of 60 mg every 6 hours during daytime hours. Patients are instructed to monitor for muscarinic side effects which may include abdominal cramping, loose stools, increased sweating, muscle twitches, and cramps. In MUSK-associated myasthenia gravis, AchEIs are less effective and can cause paradoxical worsening in some patients [91]. As a general rule, anticholinesterase therapy should be temporarily withdrawn immediately after establishing mechanical ventilatory to minimize respiratory secretions but should never be stopped completely when the patient is on

Table 3.7 List of drugs that should be used with caution in a patient with MG

Anesthetic agents
NM blocking agents (e.g., rocuronium, vecuronium, cisatracurium)
Antibiotics
Aminoglycosides (e.g., gentamicin, neomycin, tobramycin)
Fluoroquinolones (e.g., ciprofloxacin, levofloxacin, norfloxacin) - “black box” warning from FDA for use in MG.
Ketolides (e.g., telithromycin) – “Black box” warning from FDA for use in MG
Macrolides (e.g., azithromycin, clarithromycin, erythromycin)
Cardiovascular drugs
Beta blockers (e.g., atenolol, labetalol, metoprolol, propranolol)
Quinidine
Procainamide
Other medications
Botulinum toxin
Magnesium
Chloroquine
Hydroxychloroquine
D-penicillamine
Statins (e.g., atorvastatin, pravastatin, rosuvastatin, simvastatin)
Iodinated radiologic contrast agents
Corticosteroids
Desferrioxamine
Immunotherapy
Immune checkpoint inhibitors (ICIs) – e.g., nivolumab and pembrolizumab

NIV. These agents can later be restarted prior to attempts at weaning mechanical ventilation in patients recovering from myasthenic crisis.

Rapid immunological therapies for myasthenic crisis are plasma exchange (PLEX) and intravenous immunoglobulin (IVIG). Both PLEX and IVIg have been shown to accelerate recovery in patients with MG exacerbation, and administration of either of the two options is considered the standard of care for management of myasthenic crisis. The choice between PLEX and IVIg is dependent on patient's profile including co-morbidities, cost issues, availability, and adverse effects. PLEX is given every other day for a total of 5 sessions over 10 days, whereas IVIg administration is given at a dose of 0.4 mg/kg for 5 consecutive days. PLEX is considered to have a more rapid effect than IVIg and is considered the choice of therapy in patients who do not improve, are worsening, or are have severe complications. IVIg is usually avoided in elderly population or patients with co-morbidities like heart failure to avoid volume overload. Various studies including RCT and retrospective studies have shown similar efficacy of PLEX and IVIg in patients with moderate to severe MG including myasthenic crisis [92–96].

Corticosteroids are recommended as a first-line agent for use in MG and are the most effective oral immunosuppressive agent. Since the effects of both PLEX and IVIg are relatively rapid in onset and short lived, all patients with myasthenic crisis should be started on corticosteroids after initial therapy. Typically, they are started at a low dose of 10–20 mg/day with slow up-titration by 5–10 mg every 3 days to a maximum PO dose of 60–100 mg/day [97]. Another dosing regimen consists of starting IV methylprednisolone at a dose of 500–1000 mg/d for 5 days followed by 0.8 mg/kg/d IV until the patient is able to swallow pills safely [98]. Physicians should introduce corticosteroids cautiously in non-intubated patients as it can precipitate weakness in approximately one-third of patients [99].

A steroid-sparing immunosuppressant should also be introduced along with corticosteroids during the period of hospitalization in patients with severe exacerbation or myasthenic crisis, as it has shown to reduce the steroid dose and the risk of recurrent relapses [100].

Azathioprine is the most widely most widely accepted steroid-sparing immunosuppressant used for MG with response rates ranging from 70% to 91% [101]. Other steroid-sparing immunosuppressant agents that can be used include: mycophenolate, methotrexate, cyclophosphamide, and less commonly cyclosporine [102]. Rituximab, a genetically engineered chimeric mouse–human monoclonal antibody directed against CD20, has been recommended for use as an early therapeutic option in MuSK positive MG patients who do not respond to prednisone [103].

Prognosis and Complications

The most common complications seen in patients with myasthenic crisis include deep vein thrombosis, sepsis, congestive heart failure, cardiac arrhythmias, and cardiac arrest [104, 105]. The overall in-hospital mortality rate for MG patients has reduced over the years down to 2.2% and 4.47% in patients with MG crisis. Patients with advanced age and respiratory failure requiring mechanical ventilation are at higher risk of death [69].

Botulism

Clostridium botulinum is the most common infectious cause of muscle weakness causes due to production of botulinum toxin.

Epidemiology and Pathogenesis

The clinical manifestation of botulism results from the action of botulinum toxin at the neuromuscular junction which leads to the toxin's inhibition of acetylcholine release leading to progressive weakness [106]. Adults are less prone to developing botulism than the infant population because following infancy, the gut is resistant to colonization by *Clostridium botulinum* and the only condition in which an adult can get foodborne botulism is by achlorhydria, postoperative state, and gastrointestinal diseases.

Symptoms and Signs

- It commonly presents as rapid onset of descending muscle weakness accompanied with bulbar dysfunction [106].
- Respiratory failure as a result of progressive muscular weakness is the most common cause of death.

Diagnosis

- History of infected wound or consumption of contaminated food (especially in pediatric population) plays a key role.
- Electrodiagnostic studies including repetitive nerve stimulation with the demonstration of an incremental response on rapid frequency are helpful in confirmation of the diagnosis.
- Isolation of toxin on analysis of serum or feces is also considered adequate.

Management

- Antitoxin administration is the most important step after the diagnosis of botulism is made. Equine-derived heptavalent botulinum antitoxin is used in adults with the nominal potency values to be 7500 U anti-A; 5500 U anti-B; 5000 U anti-C; 1000 U anti-D; 8500 U anti-E; 5000 U anti-F; and 1000 U anti-F.
- Patients with wound-associated botulism should undergo extensive wound debridement with tetanus immunizations based on their last immunization. Penicillin G should be administered in these patients, and in cases with penicillin allergy, metronidazole should be initiated instead.
- Regular monitoring of vitals, arterial blood gas measurements, pulse oximetry, and spirometry is necessary. Intubation should be considered in patients with less than 30% of predicted vital capacity [107–110].

Muscle

Polymyositis

Polymyositis is an idiopathic inflammatory myopathy (IIM) which is considered to be the rarest subtype [111–113].

Epidemiology and Pathogenesis

Polymyositis has a subacute onset with variable progression [114]. The disease is known to be the rarest of all idiopathic inflammatory myositis and constitutes approximately 5% of all known cases of myositis [111–113].

Polymyositis is said to be caused due to the inflammatory damage exerted by the invasion of muscle fibers by CD8+ T cells which when get in contact with muscle fiber lead to exertion of their cytotoxic granules that are laden with perforin and granzyme B while clonally expanding within the muscles [115–121]. Recent studies have also report a clonal expansion of B cells [120, 121]. Endomysial CD8+ T cells and with an upregulation of MHC class I are a key pathological finding in patients with polymyositis [111, 122].

Clinical Signs and Symptoms

- Symmetric, proximal muscle weakness that worsens gradually over months [123, 124].
- Muscle atrophy resulting due to weakness and eventual disuse may or may not be present.

Diagnosis

- Laboratory tests including CK-MB and troponins show an upgoing trend due to muscle injury and myocarditis.
- The diagnosis of polymyositis should be made only after ruling out all other IIM subtypes.

Management

The goal of managing cases of poly/dermatomyositis is to improve muscle strength and avoid any extra-muscular manifestations of this disease.

- Systemic glucocorticoids are considered to be the mainstay of drug naïve patients. No standard dosing regimen exists for administration of systemic glucocorticoids, but the initial dose that the patient is started on is high to control the disease and the dose is tapered slowly to a minimum so that the lowest dose can be used for maintenance therapy [125].
- In cases where glucocorticoid therapy fails or an adjuvant is added, a glucocorticoid sparing agent can be used. The available options include azathioprine, IVIg, and hydroxychloroquine (known to be effective in controlling skin manifestations but not muscle weakness [126–128].
- In cases with extra-muscular manifestations, strength and aerobic exercises are recommended. For patients with dysphagia and nasal regurgitation due to esophageal weakness, speech therapy, along with use of nasopharyngeal or gastric feeding tube, is necessary to avoid aspiration. Use of prophylactic antibiotics should be considered in these patients.

Dermatomyositis

Dermatomyositis is another subtype of IIM which presents with both proximal muscle weakness with skin manifestations.

Epidemiology and Pathogenesis

- It is considered to be the second most prevalent IIM with the prevalence in the USA to be 1–6 patients per 100,000 persons [129].
- Dermatomyositis is theorized to be caused due to a humorally mediated autoimmune attack where the endomysial capillaries serve as an antigenic target leading to activation of complement cascade and deposition of membrane attack complexes (MAC) deposition [130–133].

Clinical Signs and Symptoms

- Distinct skin eruptions (Gottron's papules and heliotrope eruptions) are pathognomonic features of dermatomyositis. A poikiloderma on the lateral aspects of the thighs (Holster's sign) is also seen in patients with dermatomyositis [134–136].
- Other systemic manifestations: CVS (arrhythmia, myocardial infarction), gastrointestinal (esophageal weakness leading to dysphagia and nasal regurgitation), respiratory system (interstitial lung disease) [137–140].

Diagnosis

- Cutaneous manifestations mentioned above are pathognomic and hallmark features of dermatomyositis.

Management

- The management of dermatomyositis involves the steps taken to manage polymyositis and managing the skin manifestations in addition.
- The management of skin manifestation includes the usage of glucocorticoids, azathioprine, and methotrexate. Other measures include the liberal use of sun screens and sun protective clothing to avoid exposure of skin to sun. A topical formulation of tacrolimus is used in refractory cases.

Necrotizing Myositis

Necrotizing myositis is a soft tissue infection characterized by systemic signs and tissue destruction leading to significant morbidity and mortality. The most common organism implicated is group A streptococcus. The infection is usually preceded by penetrating trauma, laceration, blunt trauma, recent surgery, or a breach in skin or mucosa [141–143].

Epidemiology and Pathogenesis

Necrotizing myositis is a type of necrotizing soft tissue infection which is characterized by invasion of muscle by Group A streptococci (GAS) due to a breach of skin covering the soft tissue leading to fever, muscle weakness, and eventual muscle death followed by septicemia [143, 144]. It is a rare soft-tissue infection with a literature review having reported only 21 cases from 1900 to 1984 occurring in patients between the ages of 30 years and 60 years. Most cases involve a single

muscle group although hematogenous spread can lead to involvement of two or more muscle groups [145]. A majority of patients with necrotizing myositis also have a coexisting fasciitis owing to the proximity between the anatomical structures [145].

Clinical Signs and Symptoms

The presentation of necrotizing myositis is usually acute in nature and follows an inciting event by a few hours. Clinical signs and symptoms include:

- Erythema of overlying skin. The color of overlying skin can change to darker shades as the disease progresses.
- Edema extending beyond erythemic boundaries.
- Pain out of proportion to examination findings.
- Fever with other systemic manifestation of an infection, including tachycardia, malaise, and myalgias, is common.
- Other uncommon manifestations include crepitus, skin bullae, necrosis, or ecchymosis.

Diagnosis

- Clinical examination and a history of triggering events are important clues to this life-threatening disease.
- Laboratory findings show elevated leukocyte count, creatinine kinase, aspartate aminotransferase, lactate levels, and inflammatory markers (ESR and CRP). Decreased levels of sodium and metabolic acidosis are also seen.
- CT scan findings show the involvement of muscle and presence of gas in soft tissue.
- The definite diagnosis of necrotizing myositis is made during surgical exploration where the skin, subcutaneous tissue, fat, and muscles are examined. Intraoperative specimens of muscle are sent for pathological and microbiological analysis to confirm the diagnosis.

Management

- Necrotizing myositis is a surgical emergency and the first step in any suspected case of necrotizing myositis should be immediate surgical debridement. Aggressive debridement of affected tissue should be done to ensure that the infection does not progress to involve healthy tissue. In severe cases involving extremities, amputation should be considered to control the infection [144, 145].
- Empiric antibiotic therapy is essential to control the infection. A widely accepted regimen is pairing antibiotics with activity against methicillin-resistant *Staphylococcus aureus* (such as vancomycin or daptomycin) and clindamycin. Other options include carbapenems (such as imipenem and meropenem) and beta lactam- beta lactamase inhibitor combinations (such as piperacillin – tazobactam, ampicillin – sulbactam, and ticarcillin – clavulanic acid).
- Antibiotic therapy should be tailored depending on the culture and sensitivity results accordingly [144–146].

Miscellaneous

Mercury Poisoning

Mercury exists in three forms – elemental, inorganic, and organic. All three forms are capable of causing toxicity. Of these the organic form is considered notorious for causing neurological symptoms. The most common source of exposure to organic mercury is ingestion of fish.

However, the symptoms of organic mercury toxicity lead to paresthesias, constriction of visual field, malaise, and deafness rather than frank motor weakness. The neurological manifestations still make mercury poisoning an important differential to consider in cases of rapidly progressive weakness because of the overlapping features that it has with other causes.

Tetrodotoxin-Induced Paralysis

Tetrodotoxin is a potent neurotoxin which is found in a variety of animals including but not limited to puffer fish, poison dart frogs, the Californian newt, and trumpet shell. The most common cause of tetrodotoxin induced paralysis is due to ingestion of puffer fish which is also known as blowfish or globefish and is found in both freshwater and salt water environments.

Pathology

Tetrodotoxin causes muscle weakness and eventual paralysis by the blockade of sodium channels selectively affecting the spike-generating process of sodium channels and spares the resting and the steady-state voltage [147].

Clinical Signs and Symptoms

Symptom onset occurs within 30 min of ingestion [148].

- Oral paraesthesias of lips and tongue are generally the first manifestation.
- Gastrointestinal symptoms include nausea, vomiting, and abdominal pain.
- Severe numbness and paresthesias involve the limbs
- Salivation and diaphoresis
- Bradycardia, hypotension refractory to management
- Fasciculations
- Weakness, incoordination, hyporeflexia, and eventually muscle paralysis
- Respiratory insufficiency, cyanosis
- Complete cardiovascular and respiratory collapse is the cause of death.

Diagnosis

History of ingestion of tetrodotoxin-containing species most commonly with the above-mentioned features points to the diagnosis.

Management

The treatment of tetrodotoxin poisoning consists of supportive care [145–147].

- Although there is no established evidence for use of gastric lavage and activated charcoal in these cases, a school of thought advocates the use of these two strategies if the patient presents within 1 hour of ingestion considering the poor outcomes associated with the poisoning and limited supportive care that can be administered in these cases.
- Neostigmine is also known to partially reverse the paralysis caused due to tetrodotoxin ingestion.

Tick Paralysis

Tick paralysis is an uncommon cause of rapidly progressive weakness and has been found to affect people in North America particularly in the western regions and Australia. Although quite easy to manage and treat, if undiagnosed, tick paralysis can prove to be a cause of significant mortality [149]. The species of tick known to cause most cases of human tick paralysis in North America are *Dermacentor andersoni* and *Dermacentor variabilis* [150, 151].

Although the exact mechanism of muscle paralysis in case of tick bite remains unknown, the most common theory involves the interruption of sodium flux across axons particularly nodes of Ranveir [152]. This interruption of neural transmission through axons leads to a block in conduction thereby leading to muscle weakness [153].

Clinical Signs and Symptoms

Symptom onset occurs 4 to 7 days after the attachment of a female tick to the human body.

- Paraesthesias with fatigue are the presenting symptom although sensory examination is normal in these patients.
- Weakness follows sensory symptoms and may lead to unsteady gait.
- Rapid ascending paralysis after weakness onset is a defining feature.
- Respiratory paralysis is the most common cause of death in severe and untreated cases.

Diagnosis

Tick paralysis should be considered when a patient arrives with sudden and relatively rapidly evolving muscular weakness with no fever, normal sensory examination, and vital signs. A history of hiking in the woods is a vital clue when the patient's history is taken.

Management

The most important step in the management of a suspected case of tick paralysis is the examination of the patient's body with special attention to skin folds and scalp for tick.

– Prompt removal of tick from the body resolves the paralysis within a few hours.
– In some cases, the paralysis may worsen in the first 24–48 hours following tick removal. This is true especially for the *Ixodes holocyclus* ticks. In these cases, the patient should be observed with special attention to respiratory rate.
– Mechanical ventilation should be considered in cases where the paralysis is severe or worsening in the first 48 hours after removal of tick [154].

Hypokalemia

Potassium is one of the key electrolytes in our body playing a vital role in the cardiovascular, musculoskeletal, and the renal system. Table 3.8 mentions the most common causes of hypokalemia.

Clinical Signs and Symptoms

– Muscle weakness presents in severe cases when levels of potassium fall below 2.5 mEq/L [155].
– Muscle cramps are often the first symptom that affects lower limbs first as compared to other parts of the body.
– Muscle weakness starts in the lower limbs and evolves to include the trunk and upper extremities.
– Severe cases present with acute muscle paralysis.
– Respiratory muscle weakness eventually leading to respiratory failure is the cause of death in severe cases

Table 3.8 The different causes and mechanisms of how hypokalemia can present in patients

Causes of hypokalemia
Genetic causes
Hypokalemic periodic paralysis
Cystic fibrosis
Liddle, Bartter, and Gitelman syndrome
Decreased potassium intake
Low calorie diets
Increased intracellular transport
Insulin administration post diabetic ketoacidosis
Administration of endogenous catecholamines, myocardial infarction, head injury, or theophylline toxicity
Drug ingestion: Albuterol, terabutaline, ephedrine, pseudoephedrine, diuretics
Metabolic/respiratory alkalosis
Increased loss
Diarrhea
Acute colonic pseudo-obstruction
Polyuria
Renal tubular acidosis
Other electrolyte abnormalities – hypomagnesemia
Other causes – plasmapheresis, dialysis

Diagnosis

Serum chemistry with determination of electrolytes is an essential laboratory test that points to a decrease in potassium levels.

Electrocardiogram findings that point toward hypokalemia include depressed ST segment, decreased amplitude of T waves, and an increased amplitude of U waves, which should alert a physician toward evolving hypokalemia. Cardiac arrhythmias are commonly seen at dangerous low levels of serum potassium and require urgent attention [156, 157].

Management

The goal of managing cases of hypokalemia include prevention and treatment of life-threatening complications including paralysis, rhabdomyolysis, and diaphragmatic weakness, managing the potassium deficit and correct the underlying cause of hypokalemia.

– Potassium Repletion:

Potassium bicarbonate is the formulation of choice in cases where hypokalemia is associated with renal tubular acidosis and diarrhea while phosphate salts are used in cases of type 2 renal tubular acidosis and phosphate wasting. Chloride formulations of potassium are considered for all other cases. Intravenous potassium should be considered in patients who have severe hypokalemia (serum potassium less than 2.5–3.0 mEq/L). Table 3.9 denotes the potassium replacement protocol involving both powder- and injection-based interventions depending on the level of potassium.

Other supportive measures include:

– Careful and serial monitoring of potassium levels.
– Regular EKG monitoring to assess cardiovascular manifestations of hypokalemia and manage arrhythmia accordingly.
– Mechanical ventilation or intubation should be offered in cases of respiratory failure

Table 3.9 Adult potassium (using powder packets) replacement protocol

Potassium levels	Potassium chloride 20 mEq powder packets	Potassium chloride injections
3.7–3.9	60 meq oral/per tube once	20 meq IVPB × 1 dose
3.3–3.5	40 meq oral/per tube q2h × 2 doses	20 meq IVPB q2h × 2 doses
2.9–3.2	60 meq oral/per tube q2h × 2 doses	20 meq IVPB q2h × 3 doses
2.5–2.8	40 meq oral/per tube q2h × 3 doses	40 meq IVPB q2h × 3 doses
2.0–2.4	60 meq oral/tube q2h × 3 doses	Laboratory investigation recommended after last dose
<2.0	Both IV and oral repletion needed with repetition of laboratory investigations after the last dose. If the patient can tolerate PO, provide food or milk	

Ref: University of Missouri Neurocritical care unit electrolyte replacement protocol. *meq* milliequivalent, *PO* per oral, *q2h* every 2 hours, *IVPB* intravenous piggy bank (i.v. short-term infusion)

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Cardiac Complications Associated with Neuromuscular Diseases

4

Raghav Govindarajan and Pretty Sara Idiculla

Introduction

Neuromuscular diseases (NMDs) are diseases that affect the peripheral nervous system anywhere from the motor neuron to the muscle [1]. It is considered a broad diagnosis as they can affect different organ systems and cardiac involvement in particular is a common manifestation. Cardiac disease is associated with a high morbidity and mortality and the presentation depends on the type of NMD as well as the structure and function of the heart that is affected. Cardiomyopathy due to involvement of the myocardium, arrhythmias when the conduction system gets affected or even sudden cardiac death are the usual heart disease manifestations seen in these patients [2]. Neuromuscular specialists need to be familiar with these cardiac manifestations, and be able to identify associations, evaluate, provide appropriate treatment, and recommend routine follow-up. A better understanding of the etiopathogenesis and natural course of these disease entities enable the development of better therapeutic modalities and advanced surveillance technique development in the future. The early detection of these cardiac diseases may help institute early cardioprotective treatment thereby reducing the associated morbidity and mortality.

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Neuromuscular Diseases with Cardiac Involvement

NMDs with cardiac involvement that are discussed in this chapter include:

- Dystrophinopathies
- Emery–Dreifuss muscular dystrophy
- Facioscapulohumeral muscular dystrophy
- Limb-girdle muscular dystrophy
- Myotonic dystrophy
- Barth syndrome
- Friedreich ataxia
- Congenital myopathies
- Myofibrillar myopathies

Dystrophinopathies

Disease Subtypes

Dystrophinopathies are a spectrum of diseases that occur from mutations affecting the dystrophin gene, and these constitute three major phenotypes:

– Duchenne muscular dystrophy (DMD)
– Becker muscular dystrophy (BMD)
– X-linked dilated cardiomyopathy (XLDCM)
– Manifesting carriers of dystrophin gene mutation (MCD)

Inheritance

DMD and BMD are different entities of the same genetic mutation, and the latter is a milder form of the disease. XLDCM is a subtype that occurs as a result of the same mutation, and there is isolated involvement of the heart muscle. All these different phenotypes are inherited in an X-linked recessive (XLR) pattern and occur due to mutation of the dystrophin gene on the Xp21 locus of the X chromosome [3].

Pathophysiology

Dystrophin is a sarcolemmal protein involved in providing cytoskeletal support to the myofibers helping in stabilization during muscle contraction [4]. The different isoforms are expressed in different tissues like the striated skeletal muscle, smooth muscle, cardiac muscle, as well as the brain, retina, and peripheral nerves [5]. These patients develop muscle weakness due to abnormal muscle contraction and subsequent degeneration, which eventually becomes irreversible [6]. When the mechanical stress-induced injury occurs in the heart muscle, there are muscle degeneration,

fibrosis, and atrophy of the left ventricular wall, resulting in cardiomyopathy [7]. Beta receptors are abundant in the heart, and its activation results in tachycardia and increases myocardial contractility. The dystrophic heart is prone to autonomic dysfunction thereby increasing adrenergic stimulation of the heart, contributing to development of arrhythmias [8].

Dystrophin production is absent in DMD while there is reduced or partial production in those affected by BMD. In XLDCM patients, there is lack of dystrophin protein exclusively found in the cardiac muscle, with mild to no skeletal muscle involvement. Carriers of the dystrophin gene mutation are asymptomatic females that may manifest the disease with varying severity due to random inactivation of the normal X chromosome.

Epidemiology

DMD is one of the most common forms of muscular dystrophy, and the epidemiologies of various dystrophinopathies are as mentioned in Table 4.1.

Clinical Features

Dystrophinopathies affect the skeletal and cardiac muscles, and the cardiac involvement is discussed individually as it is the main focus of this review. DMD patients have delayed motor milestones, proximal muscle weakness, and calf pseudohypertrophy. Respiratory failure is a common cause of death, especially in untreated patients. Intellectual disability, behavioral, social, and cognitive abnormalities are also prevalent in affected individuals [14]. BMD has clinical symptoms presenting at a much later age with the limb-girdle weakness being usually the first sign of involvement [15]. In XLDCM, patients have exclusive cardiac involvement, and the only form of muscle involvement is a mild subclinical myopathy [16]. The disease spectrum in the carriers varies from mild late-onset proximal muscle weakness, myalgia, or cramps to severe disabling disease [13].Table 4.2 describes the different types of cardiac manifestation in dystrophies.

Table 4.1 Types of dystrophinopathies

Type	Incidence	Prevalence	Age of presentation
DMD	1 in 3600–1 in 6000 live male births [9]	6 in 100,000 males [10]	4–5 years [11]
BMD	1/18,000 live male births [9]	2.4 per 100,000 in the general population [10]	5–15 years [11]
XLDCM	Rare	–	Late teens–Early 20s [12]
MCD	8–22% [4]	–	2 years–late 40s [13]

Table 4.2 Cardiac manifestations in dystrophinopathies

Dystrophinopathy	Features of cardiac involvement
DMD	Dilated cardiomyopathy (DCM) is the most common cardiac manifestation in affected individuals. The occurrence of cardiac dysfunction is universal in patients >18 years old and rises with increasing age as well as worsening skeletal muscle function Due to early immobilization in these patients, the symptoms of cardiac failure are subtle. Progressive congestive heart failure from the DCM may be responsible for increased mortality in approximately 15% of affected individuals [17] They can also develop conduction abnormalities, ventricular more than supraventricular arrhythmias, and they have an increased occurrence in patients with moderate to severe cardiac dysfunction as well as with increasing age despite the cardiac function [18] Sudden cardiac death can occur as a result of the arrhythmias itself or progressive cardiac muscle failure though an exact cause still remains unknown [17]. Cardiac death is observed in about 20% of DMD patients [2]
BMD	Cardiac muscle involvement in BMD is more clinically apparent as these patients are more physically active and respiratory muscle function is preserved until late in the disease. Patients are able to perform more strenuous exercise hence causing more strain on the myocardial cells Ventricular or supraventricular arrhythmias are more common in BMD patients and a 25% occurrence was noted on Holter monitoring [18] Arrhythmias and congestive heart failure can result in sudden cardiac death in almost half of the affected individuals [17] Cardiac death has been observed in approximately 50% of BMD patients [2]
XLDCM	Affected individuals have rapidly progressive DCM with congestive heart failure being the initial presentation and can also develop fatal arrhythmias [9] These patients can be harder to differentiate from BMD due to the similar age of presentation and mild skeletal muscle involvement [19] Cardiac death occurs in almost all the affected individuals [20]
MCD	The incidence of cardiac disease in female carriers is rare before the age of 16 years and becomes more evident with increasing age [21] Cardiac involvement in carriers is progressive with the prevalence of DCM varying from 3% to 84% [22] Carriers of DMD/BMD demonstrated reduced ejection fraction and also showed features of myocardial fibrosis [23] Carriers of XLDCM have a late onset of slowly progressing cardiac dysfunction [24]

Diagnostic testing in dystrophinopathies

Diagnostic test	Description
Creatine kinase (CK) levels	There is marked elevation of CK levels, often more than 10x the normal values due to the ongoing muscle damage [25]

(continued)

Diagnostic test	Description
Electrocardiogram (ECG)	ECG changes are usually the first sign of cardiac involvement in these patients and can be observed as early as 6 years of age Initial changes detected include prominent Q waves in the lateral (I, aVL) or inferolateral and apical (II, III, aVF, V5-V6) leads, high R waves in V1-V3, dysmorphic or inverted T-waves, prolonged corrected QT interval, short PR interval, and right ventricular hypertrophy. In advanced disease, various rhythm abnormalities can be detected in these patients [26] Studies show that the presence of QT changes in DMD patients can identify those at a higher risk of cardiac death [27] Since ECG changes occur very early in the disease, it is not a useful tool for the progression of cardiomyopathy in DMD patients [28]
Echocardiography (ECHO)	ECHO in DMD patients show myocardial thickening, abnormal wall mobility, left ventricular enlargement, systolic and diastolic dysfunction. The posterobasal part of the left ventricle is the initial area that undergoes fibrosis followed by the interventricular septum and right ventricle ECHO is quick, widely available, and cost-effective; however, in advanced disease where patients develop scoliosis and chest wall abnormalities, it can become challenging to perform the test [29] ECHO is dependent on factors like the acoustic window and the need for an operator to perform the procedure [10] A tissue Doppler ECHO helps to determine the progression of cardiac dysfunction, while the use of myocardial strain imaging can be useful for early detection of subclinical cardiomyopathy [30] However, studies have also shown that cardiac MRI with late gadolinium enhancement is superior to a 2D ECHO and tissue Doppler for early assessment of cardiac function [31]
Cardiac magnetic resonance imaging (MRI)	CMR is the preferred imaging modality due to its ability to assess morphology, function, and tissue characteristics of the heart. It helps assess ventricular volumes, ejection fraction, as well as both focal and diffuse myocardial fibrosis They can be used for serial evaluation of patients due to their operator independence as well as their property of reproducibility [32] Abnormal global and segmental circumferential strain is noted in DMD patients, and myocardial strain precedes left ventricular dysfunction and subsequent fibrosis [33] The noninvasive technique of myocardial delayed enhancement helps to evaluate myocardial fibrosis which is frequently found in DMD indicating that cardiac involvement begins at earlier stages of the disease [34] The use of late gadolinium enhancement to assess fibrosis is an important prognostic factor because even the presence of a small amount of contrast in the myocardium increases the risk of a major cardiac adverse event [35]. Cardiac MRI becomes particularly useful in the advanced stages of the disease where the patients are limited because of the scoliosis and obesity [36] MRI can be challenging in patients who cannot be positioned comfortably due to contractures, and even though sedation can help with the problem, cardio-respiratory compromise can impact the decision-making process [37]. Other drawbacks include the increased time and cost involved with the procedure and the lack of easy availability of equipment and expertise [10] Cardiac MRI is a sensitive diagnostic tool for early detection of cardiac dysfunction even when the ECHO can be normal. The importance is that early institution of treatment can help delay the hypertrophic changes, cardiovascular events, and subsequent cardiac remodeling in DMD patients [38]

(continued)

(continued)

Diagnostic test	Description
Muscle biopsy	Earlier stages show characteristic features like varying fiber size, areas of necrosis, splitting fibers, cardiomyocyte hypertrophy, nuclear internalization, and increased connective tissue Later stages show extensive fibrosis, fat replacement, and muscle atrophy Immunostaining with anti-dystrophin antibodies shows absent dystrophin in DMD patients, while Western blot helps in dystrophin quantification and is highly specific [39]
Genetic testing	Genetic diagnosis is the confirmatory test for diagnosis of DMD. It is the basis of treatment and aids prenatal diagnosis and genetic counseling Techniques like multiplex ligation-dependent probe amplification technology (MLPA) help detect the gene mutations, and "next-generation" sequencing technology (NGS) or Sanger sequencing can be used to detect smaller mutations Polymerase chain reaction (PCR) is used to exclude false-positive tests associated with MLPA [40]

BMD:

Diagnostic test	Description
CK levels	BMD patients can rarely have asymptomatic elevation of CK levels as well as can have very high levels of serum CK because of their ability to perform strenuous exercise resulting in rhabdomyolysis, and subsequent myoglobinuria [41]
ECG	The ECG changes in BMD patients occur at a different time and to different extent in comparison to DMD patients. However, the pathological changes are fully evolved before the patient develops any changes observed on cardiac imaging [24]
ECHO	BMD patients develop ECHO findings similar to DMD patients associated with severe cardiac dysfunction [9]
Cardiac MRI	MRI is the preferred modality for early detection of cardiac dysfunction. Cardiomyopathy is the most common cause of mortality in patients with BMD, making assessment of cardiac function important in these patients. The characteristics observed on MRI are similar to that of DMD patients [34]
Muscle biopsy	Features observed on biopsy are similar to DMD; however, immunostaining and Western blot detects reduced to normal amounts of dystrophin [39]
Genetic testing	Genetic diagnosis is the confirmatory test, and MLPA is used for detection of the gene mutations while NGS is performed in MLPA-negative samples [40]

XLDCM:

Diagnostic test	Description
CK levels	In most patients, there is subclinical myopathy resulting in mild to moderate elevation in serum CK levels [9]
ECG/ECHO	Patients can have ECG and ECHO features similar to that detected in DMD/BMD patients [42]
Cardiac MRI	MRI is considered the diagnostic modality of choice for assessment of cardiac function even at earlier stages of the disease, and the features resemble DMD/BMD patients. This becomes particularly important due to the progressive nature of the condition [7]
Muscle biopsy	Biopsy shows minimal changes in comparison to DMD/BMD like variable fiber size, mild necrosis, atrophy, and nuclear internalization in cells [43]. Immunostaining shows normal to minor reduction in dystrophin levels [39]
Myocardial biopsy	Myocardial fibrosis and fat replacement of cardiac muscle with loss of striation, vacuolation, or nuclear fragmentation indicate atrophic changes. Immunostaining [9]
Genetic testing	Genetic diagnosis is definitive, and analysis is done using PCR or MLPA, which is more sensitive at detecting the mutations [44]

MCD: Diagnosis of DMD/BMD carriers is based on clinical symptoms, family history, biochemistry markers, echocardiography, pathology, molecular genetic analysis, and linkage-testing.

Diagnostic test	Description
CK levels	Elevated CK levels can be observed in carrier females and is an unreliable indicator to assess the risk of cardiomyopathy in these patients [23]
ECG/ECHO	Since cardiomyopathy can occur in these patients, it is essential that these patients be screened regularly [45]
Cardiac MRI	MRI can help assess the myocardial function in these patients, and studies have shown a pattern of fibrosis similar to that observed in DMD patients [46]
Genetic testing	Genetic diagnosis is essential in first-degree relatives of affected individuals to identify potential carriers which can aid risk stratification in subsequent pregnancies [38]. Molecular genetic analysis and linkage-testing helps determine carriers with a positive family history [47]

Treatment

Treatment protocol for cardiac manifestations in dystrophinopathies

Dystrophinopathy	Description
DMD	Advancements in managing DMD patients like steroids use, stabilizing scoliosis, and strong respiratory support have improved the survival to late 20s to early 30s [48] The initiation of cardiac treatment in DMD patients is a debatable topic; however, studies show that there is a greater impact noted when therapy is instituted earlier in the disease even before the patient becomes symptomatic from the heart disease [49] Current guidelines recommend starting treatment before or by 10 years of age angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). These are older classes of drugs that have shown to improve cardiac function and hence increasing the patient's survival. ACEI are the primary option and in case of intolerance ARBs are used though they are equally effective. The ARBs have the property of protecting the heart cells from damage that can occur due to increased strain during periods of acute exertion [8] DMD patients are prone to arrhythmias which occur from the cardiac dysfunction, and the benefits of using beta-blockers in DMD patients are mixed [50]. Though studies show a clear improvement with use of these drugs in patients with reduced ejection fraction, it is not recommended to be used in DMD cardiomyopathy until these patients develop detectable arrhythmias [51] Mineralocorticoid antagonists like eplerenone and spironolactone are useful in DMD patients as aldosterone promotes cell death, hypertrophy, and fibrosis in these patients. A clinical trial involving DMD patients already on ACEI/ARB therapy showed a moderate improvement in the left ventricular strain, ejection fraction, and chamber dilation in those who received eplerenone compared to patients who didn't receive it [52]. The time of initiation and the long-term benefit of using these drugs in DMD patients are still not known due to the lack of confirmatory studies Corticosteroids are the earliest form of therapy in DMD patients that interfere with the natural course of the disease allowing patients to stay ambulatory for longer periods of time by prolonging their muscle strength [53]. Studies show that steroids can have cardioprotective effect in DMD patients that includes preserving cardiac function, reduce fibrosis, hence improving survival [54]. Vamorolone is a dissociative steroid, a new class of drug that is under study. It is said that it can deliver similar effects of corticosteroids while causing minimal side effects associated with the long-term use of the latter [55] Gene therapy is a curative approach that has begun to gain importance in recent years because it aims at restoring functional dystrophin. This evolving targeted form of treatment is highly complex and is particularly challenging to achieve the desired efficiency [8]. Some of these emerging therapies include dystrophin gene replacement, gene-editing strategies, and exon skipping The use of implantable cardiac defibrillators in DMD cardiac disease lacks any confirmatory evidence [28] Cardiac transplantation is the only definitive therapy for end-stage heart disease though, due to the progression of the disease, multi-organ involvement, and the lack of widely available donors, patients rarely are considered for transplantation. Left ventricular-assisting devices (LVAD) is an alternative to transplantation and may help resolve symptoms of cardiac dysfunction, improving quality of life. However, there are no studies that indicate that these devices prolong survival in DMD patients [56]

(continued)

Dystrophinopathy	Description
BMD	Cardiomyopathy is more severe in BMD patients, and medical therapy for heart failure is recommended in those who develop a left ventricular ejection fraction <55% [57]. When these patients develop rapidly progressing and severe cardiac disease, a heart transplant and LVAD can be lifesaving and studies have shown good clinical outcomes [58]
XLDCM	The medical therapy in XLDCM is similar to patients with DMD/BMD, and cardiac transplantation is the considered the best form of treatment for those with severe cardiomyopathy [59]. In the absence of a transplant, these patients' death may occur within 2 years of clinical presentation [25]
MCD	Currently once a baseline cardiac evaluation is made, cardiac surveillance is recommended. If these patients develop clinical symptoms, medical therapy for cardiomyopathy is indicated, and in severe disease, transplantation may be required [2]

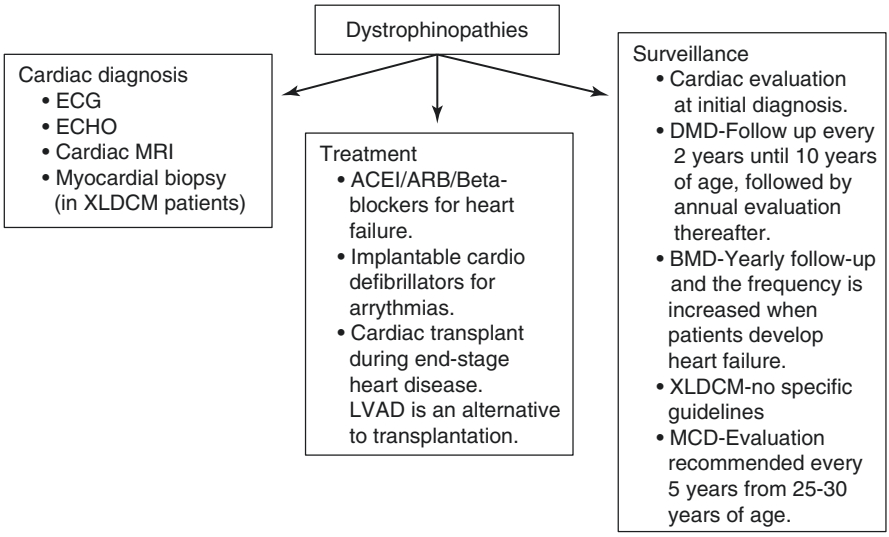
Prognosis and Surveillance

Individuals affected by any of these disease conditions can develop progressive cardiac disease, and this warrants regular follow-ups with tests like ECG and ECHO.

Cardiac surveillance in dystrophinopathies

Dystrophinopathy	Description
DMD	With the introduction of corticosteroids and supportive ventilatory devices, a noticeable improvement has been noted with the motor and respiratory outcomes in DMD patients Mortality from cardiac disease has become an emerging cause of death due to the treatment advances. Death occurs around the second to third decades of life, and since DMD is a progressive systemic myopathy, cardiac transplantation is contraindicated in these patients [60] Cardiac evaluation should be performed as soon as a patient is diagnosed with DMD, and since the changes occur at a very early age as well as is progressive, follow-up surveillance is important It is suggested that these patients undergo testing once every 2 years till the patient develops symptoms or reaches 10 years of age, after evaluation has to be performed yearly [61]
BMD	Once the diagnosis of BMD is made, frequent cardiac surveillance is indicated as these patients can have subclinical cardiac disease that can late develop into severe cardiomyopathy The current recommendation is yearly monitoring after diagnosis of BMD is made and when the frequency of surveillance is increased when symptoms of heart failure develops in these patients [57]
XLDCM	There are no specific guidelines recommended for follow-up in XLDCM patients; however, cardiac evaluation at regular intervals is recommended once the patients develop clinical symptoms [62]
MCD	Due to an elevated risk of developing cardiac adverse events in the female carriers, the American Academy of Pediatrics (AAP) recommends that these patients undergo a complete cardiac evaluation at the time of diagnosis and followed by evaluations every 5 years starting at 25–30 years of age [63] Prenatal diagnosis and genetic counseling are recommended in diagnosed carriers if they get pregnant again as it is a major part of preventing the occurrence of DMD/BMD [47] These patients are explained the benefits of reducing cardiac disease risk factors and the strategies that can be utilized to maintain a healthy lifestyle [61]

Cardiac Management in Dystrophinopathies



Emery–Dreifuss Muscular Dystrophy

Disease Subtypes

Emery–Dreifuss muscular dystrophy (EDMD) is a slowly-progressive myopathy resulting in early-onset joint contractures, skeletal muscle weakness, and cardiac dysfunction. They constitute three subtypes:

– X-linked Emery–Dreifuss muscular dystrophy (X-EDMD)
– Autosomal dominant Emery–Dreifuss muscular dystrophy (AD-EDMD)
– Autosomal recessive Emery–Dreifuss muscular dystrophy (AR-EDMD)

Inheritance

The inheritance pattern of EDMD can be X-linked or autosomal as shown below [64].

Inheritance pattern of EDMD

EDMD	Subtype	Inheritance	Gene locus	Gene product
X-EDMD	Emerin-related EDMD	XLR	Xq28	Emerin
	FHL1-related EDMD	XLR	Xq26	FHL1
AD-EDMD	LMNA-related EDMD	AD	1q11-q21	Lamin A/C
AR-EDMD	LMNA-related EDMD	AR	1q11-q21	Lamin A/C

Pathophysiology

X-EDMD patients lack the nuclear membrane protein emerin which is a type II integral protein in all muscles (skeletal, cardiac, and smooth), skin, and blood leukocytes. Lamins A/C are intermediate filaments that form the nuclear lamina in the inner nuclear membrane [65]. FHL1 is a sarcolemmal protein that plays a role in sarcomere assembly through its interaction through myosin-binding protein C [66]. These proteins have a vital role in various cellular processes, nuclear assembly, chromatin organization, gene transcription, and development signaling. The defective proteins cause alteration in these processes that result in impairment of both skeletal and cardiac muscle functioning [67].

Epidemiology

EDMD has an estimated worldwide incidence of 1 in 100,000 people of which approximately 30% is attributed to the LMNA gene, 10% to the EMD gene, and 2% to the FHL1 gene. The age of onset is usually between 5 and 10 years of age and is very rare before this age [68].

Clinical Features

EDMD subtypes have a similar clinical presentation, and it involves a classic triad of early-onset joint contractures, slowly progressive muscle weakness, and cardiac involvement. The contractures predominantly involve ankles, elbows, posterior cervical muscles, and the entire spine. Muscle weakness initially shows a humeroperoneal distribution which then goes on to involve the shoulder and pelvic girdle muscles [69].

Cardiac Involvement

Cardiac disease in EDMD occurs in the second to third decades of life, causing cardiac conduction defects, DCM, and sudden cardiac death. Arrhythmias are the most common form of cardiac involvement which can manifest as bradycardia and various degrees of atrioventricular blocks, atrial fibrillation and flutter (most common cardiac event), extrasystoles, and supraventricular tachycardia [68]. There is a subsequent atrial standstill that results in an increased risk of cardioembolic stroke and also development of cardiomyopathy that rarely results in consequent congestive heart failure. DCM is seen in EMD- or LMNA-related EDMD patients, and hypertrophic cardiomyopathy (HCM) is related with FHL1-related EDMD. Sudden cardiac death can occur from a complete heart block or from the life-threatening arrhythmias. Female carriers have a risk of developing cardiac arrhythmias and sudden death; however, skeletal muscle involvement is absent in these patients [70].

Diagnosis

The diagnosis of EDMD is based on the clinical triad and can be confirmed through various diagnostic tests as shown in Table 4.3.

Table 4.3 Diagnostic testing in EDMD

Diagnostic test	Description
CK levels	Mild-to-moderate elevation is common in the initial stages of the disease [71]
Electromyogram (EMG)	Normal nerve conduction studies with myopathic features on EMG are usually seen [68]
ECG/ECHO	ECG changes can be seen as varying degrees of heart block, or other forms of arrhythmias like atrial fibrillation and tachyarrhythmias [61]. ECHO helps to detect the presence of cardiomyopathy and any systolic or diastolic dysfunction [72]
Cardiac MRI	These patients often have pacemaker implantation to prevent sudden cardiac death; hence, the use of an MRI is limited in these patients. There is replacement of myocardium with fibrous and adipose tissue, usually involving the atrium first, the conduction system, and eventually the ventricles [73]
Muscle biopsy	Biopsy is now rarely done because of the lack of specificity. Myopathic changes including varying fiber size, mispositioned nuclei, increased endomysial connective tissue, and myonecrosis can be seen [74]
Immunodetection	Emerin is absent in almost 95% of X-EDMD and is FHL1 is absent or decreased in FHL1-related EDMD. The carriers of the disease can have varying amounts of the protein emerin or FHL1 expressed in the respectively affected individuals [68]. Lamins A/C detection in affected individuals is not a reliable test and may be just contributory evidence as the levels can be normal in affected patients [75]
Genetic testing	Genetic testing in these individuals aids confirmation of diagnosis, determine subtype of EDMD, and also help determine gene-targeted therapies. Targeted gene testing and comprehensive gene testing approaches can be utilized for this purpose [68]

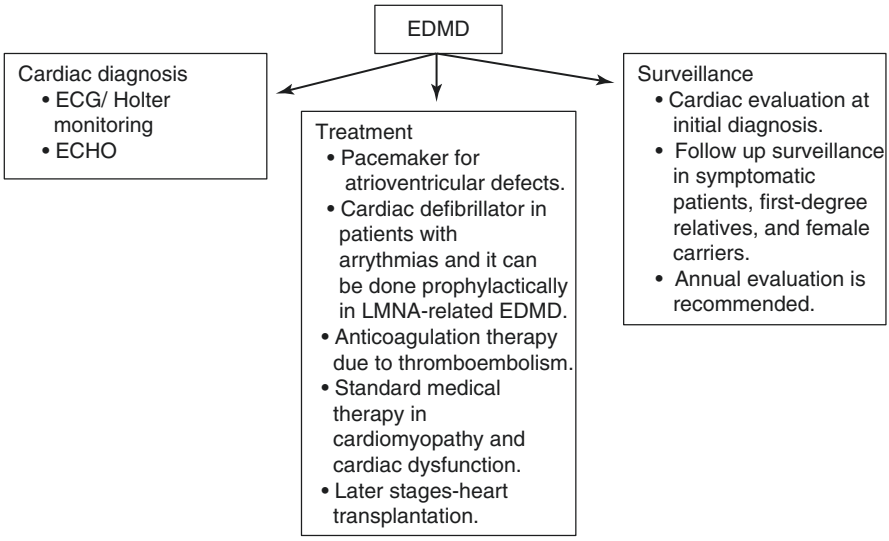
Treatment

The treatment of affected individuals is through a combined effort of multiple specialists. Orthopedic procedures to relieve contractures and spinal deformity, supportive management for cardiac involvement. Affected individuals undergo a cardiology referral for management of arrhythmias as well as to evaluate the patients for the need for a pacemaker or defibrillator [76]. Though these patients undergo pacemaker implantation, they still have a higher risk of developing ventricular arrhythmias and sudden cardiac death [77]. Implantable cardiac defibrillators are considered as a prophylaxis in patients associated with LMNA-related EDMD [78]. Since there is increased risk of cardiac thromboembolism, anticoagulation therapy is highly recommended [79]. Treatment with standard pharmacologic and non-pharmacologic therapy is recommended in those who develop cardiomyopathy and subsequent cardiac dysfunction. Heart transplantation may be indicated in the later stages of the disease; however, respiratory insufficiency and severe muscle involvement may be a contraindication to this [61]. An early detection, targeted treatment, and genetic counseling are the key to improve quality of life in affected individuals.

Prognosis and Surveillance

Patient with EDMD are generally ambulatory up to the third decade of life, and the common cause of death is the occurrence of sudden cardiac death [70]. Cardiac screening is recommended in patients affected with EDMD including the female carriers of EMD. Follow-up testing is recommended in diagnosed patients who develop arrhythmias, cardiomyopathy, and cardiac dysfunction. All patients including the first-degree relatives of EDMD patients and female carriers require regular cardiac follow-up [80]. Annual ECG evaluation and Holter monitoring is recommended for patients with any form of EDMD [37].

Cardiac Management in EDMD



Facioscapulohumeral Muscular Dystrophy

Definition

Facioscapulohumeral muscular dystrophy (FSHD) is one of the common forms of muscular dystrophy that, as the name suggests, manifest with weakness of facial, scapular, and humeral muscles which later progresses to involve trunk, lower extremities, and proximal muscles [81].

Inheritance

FSHD is inherited in an autosomal dominant (AD) fashion and is caused by a mutation in the long arm of chromosome 4 at the 4q35 gene locus that produces the double homeobox 4 (DUX4), which is a transcription factor [82].

Pathophysiology

In FSHD, there is a decrease in the microsatellite repeats in the 4q35 gene locus (<10 repeats) which results in hypomethylation, relaxing chromatin, and resulting in transcription of a normally dormant gene. DUX4 protein when mis-expressed may result in potential cytotoxicity, triggered inflammatory response, and cell apoptosis [83].

Epidemiology

FSHD has a worldwide prevalence of 2–7 in 100,000 individuals and a prevalence of 1 in 8000–15,000 individuals in the United States [84]. Women are considered to be affected at a later age compared to men due to the lower penetrance in the former [85].

Clinical Features

Patients with FSHD have a widely varying onset, progression, and severity with the common onset being late teenage or early adult years [83]. Approximately, 10% of cases have an early-onset disease (<5 years) that is associated with severe muscle weakness and patients becoming wheelchair bound in the second decade of life [86]. The patients develop progressive weakness of the facial, scapular, and humeral muscles that subsequently affects the trunk, lower extremities, and proximal muscles. Hearing loss, retinal vasculopathy, restrictive lung disease, and cardiac arrhythmias can also occur in addition to the muscle disease. The quality of life in these patients decreases with increasing severity of the disease [87].

Cardiac Involvement

Cardiac disease in the form of cardiomyopathy and arrhythmias is a rare presentation in FSHD though cardiac conduction defects are more common than structural cardiac involvement [88]. Rhythm abnormalities include bradycardia, atrioventricular conduction defects, ventricular arrhythmias, and atrial arrhythmias [89].

Diagnosis

The diagnosis is based on the clinical manifestations, a positive family history, and supported by the diagnostic testing as shown in Table 4.4.

Treatment

Treatment of FSHD involves a multidisciplinary approach since there is no approved targeted therapy for the disease condition. Physical therapy, use of assistive devices, pulmonary function testing, ophthalmological testing, screening for hearing deficits, pain management, and cardiac screening constitute the parts of management in FSHD patients [92].

Prognosis and Surveillance

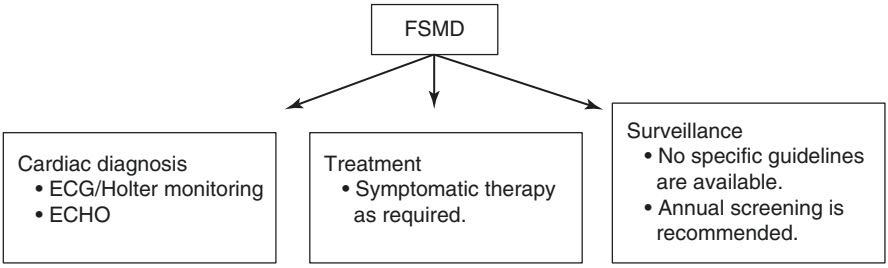
Patients with FSHD have a normal life expectancy, and the risk of becoming wheelchair bound may occur during the second decade of life, if they have an infantile onset or after 50 years of age in those with the late-onset, slow-progressive form

Table 4.4 Diagnostic testing in FSHD

Diagnostic test	Description
CK levels	CK levels are usually normal or moderately elevated than the normal limit [83]
Electromyogram (EMG)	Small, polyphasic motor units that indicate nonspecific myopathic changes is usually seen. Positive sharp and fibrillatory waves are also identified; however, they are uncommon [82]
ECG	ECG changes in FSHD include short PR interval, tall P waves, abnormal Q waves, tall T waves, conduction abnormalities from mild conduction defects to complete heart block, ventricular tachycardia, or other cardiac arrhythmias [89]
ECHO	ECHO in patients with FSHD may show hypertrophic or dilated cardiomyopathy [88]
Muscle biopsy	Myopathic changes including variation of fiber size, nuclear internalization, myonecrosis and atrophy, fibrofatty infiltration, and perivascular inflammation [90]
Genetic testing	The most common method for molecular diagnosis is by Southern blotting. Less commonly used ones are the PCR method and molecular combing technique [91]

[93]. Though it is not essential to screen asymptomatic individuals, studies suggest obtaining cardiac screening in the form of annual ECG and Holter monitoring in FSHD patients [92].

Cardiac Management in FSMD



Limb-Girdle Muscular Dystrophy

Definition

Limb-girdle muscular dystrophy (LGMD) is a genetically inherited disease condition causing progressive proximal muscle weakness with subsequent loss of muscle fibers [94]. The diagnostic criteria were defined in 2018 by the European Neuromuscular Centre which defines that the disease should be present in at least two non-related families with affected patients achieving independent walking, having elevated serum CK levels, imaging showing progressive muscular degeneration during the course of the disease, and muscle biopsy showing dystrophic changes [95].

Table 4.5 Genetic testing in LGMD

Type of LGMD	Gene locus/gene product
LGMD 1B	1q11-q23/ Lamin A/C
LGMD 2C	13q12/ γ-Sarcoglycan
LGMD 2D	17q12-q21.33/α-Sarcoglycan
LGMD 2E	4q12/β-Sarcoglycan
LGMD 2F	5q33-q34/δ-Sarcoglycan
LGMD 2I	19q13.3/Fukutin-related protein (FKRP)

Inheritance

There are more than 25 different forms of LGMD of which LGMD1 has an autosomal dominant inheritance and LGMD2 is inherited in an autosomal recessive (AR) fashion. The common forms of LGMD that have prevalent cardiac manifestations include LGMD1B, C and LGMD 2C, D, E, F, I [70]. The involved gene locus and protein produced depends on the type of LGMD as shown in Table 4.5.

Genetic Mechanisms in LGMD

Genetic mechanisms in LGMD

Type of LGMD	Pathophysiological mechanism
LGMD 1B	There is abnormal production of Lamin A/C which is also implicated in various other diseases including AD/AR-EDMD and hence has similar pathophysiological features [96]
LGMD 2C-2F	The protein products of the associated genes are collectively called sarcoglycans which forms a part of the dystrophin-glycoprotein complex that, which when mutated, produce skeletal and cardiac muscle disease [97]
LGMD 2I	FKRP are proteins that modify cell surface glycoproteins and lipids. Mutations that cause late-onset disease is characterized by elevated CK levels, recurrent myoglobinuria, and DCM [98]

Epidemiology

The overall prevalence of LGMD ranges from 3 to 10 per 100,000 individuals though the distinct subtypes is relatively rare [99] (see Table 4.6).

Clinical features of select LGMD

Type of LGMD	Cardiac manifestations
LGMD 1B	Proximal muscle weakness with increased predilection for humeral and calf muscles. Late-onset of mild contractures in elbows, ankles, hips, and neck muscles has also been noted [102]
LGMD 2C-2F	These groups of disease tend to affect predominantly the flexor group of muscles and are often rapidly progressive resulting in patients that are wheelchair bound within a few years of diagnosis [103]
LGMD 2I	Proximal lower extremity weakness, scapular winging, calf hypertrophy, and occasional tongue hypertrophy have been noted [104]. Muscular pain and myoglobinuria after exercise have also been noted in these patients [105]

Table 4.6 Epidemiology of selected LGMD

Type of LGMD	Age of onset	Prevalence
LGMD 1B	<10 years–20 years [100]	–
LGMD 2C	[a]	[b]
LGMD 2D	[a]	[b]
LGMD 2E	[a]	[b]
LGMD 2F	[a]	[b]
LGMD 2I	<10 years–>40 years [100]	Higher prevalence in North European population – 1 in 50,000 individuals [101]

[a]Sarcoglyconopathies (LGMD2C-F) has an age of onset of <10 years–20 years [100]
[b]Sarcoglyconopathies (LGMD2C-F) had an overall prevalence of 1 in 100,000 individuals with 2F being the least common among them [101]

Cardiac involvement in select LGMD

Type of LGMD	Cardiac manifestations
LGMD 1B	From the second decade of life, patients can develop progressive arrhythmias and dilated cardiomyopathy [103]
LGMD 2C-2F	Patients can have arrhythmias which can also be fatal. These patients can also develop cardiac dysfunction and heart failure [101]
LGMD 2I	Dilated cardiomyopathy with cardiac dysfunction can be noted in these patients and very few develop heart failure [70]

Diagnostic testing for select LGMD

Type of LGMD	Diagnostic tests
LGMD 1B	CK levels are about 5 times above the normal level Muscle imaging shows fatty infiltration in the lower limb muscles Muscle biopsy may show varying fiber size and dystrophic features [94] ECG and Holter monitoring are done for diagnosis of life-threatening arrhythmias ECHO imaging can help diagnose any cardiac dysfunction from cardiomyopathy [17]
LGMD 2C-2F	The CK levels are very high, more than 100x the normal limit, and muscle biopsy followed by staining may be helpful; however, genetic testing is used commonly to distinguish between the various types of sarcoglyconopathies [70] ECG changes similar to various dystrophinopathies can be identified in these patients. Ventricular tachyarrhythmias and atrial fibrillation, left ventricular hypertrophy are some changes that can be noted in these patients [106] ECHO can show abnormal systolic and diastolic dysfunction as well as cardiac enlargement [107] MRI of the muscles show fibrofatty infiltration of lumbar paraspinal, gluteal, thigh (with distal vasti muscles sparing), and calf muscles [108]
LGMD 2I	A uniform elevation of serum CK levels is noted in these patients and is usually about 10× the normal limit [94] Muscle biopsy show dystrophic changes with decreased glycosylated α-dystroglycan [109] ECG for determining any arrhythmias and ECHO to detect dilated cardiomyopathy is performed Cardiac MRI can detect the involvement and extent of myocardial fibrosis. Skeletal muscle MRI helps determine fibrofatty infiltration in the lower limb muscles with conservation of anterior thigh muscles [94]

Treatment

The basic guidelines that have been implicated in the treatment of LGMD include:

- Multidisciplinary neuromuscular clinics
- Involvement and evaluation by specialists from various specialties like pulmonology, orthopedics, and cardiology
- Access to physical, occupational, speech therapists, as well as orthotics and assistive medical devices
- Genetic testing and subsequent counseling
- Counseling and providing encouragement to lead an active and fruitful life [97]

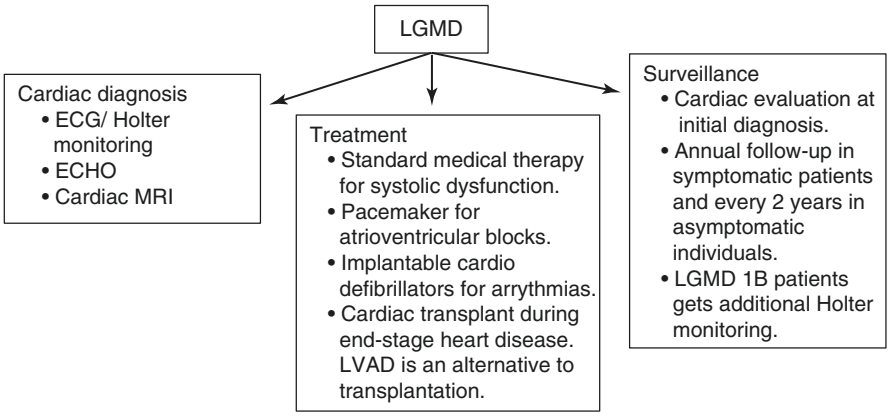
Early cardiological evaluation of these patients is important, and prompt treatment has to be instituted to prevent complications of fatal arrhythmias and heart failure. These include use of pacemakers, implantable defibrillators, and transplantation in the last stages. Systolic dysfunction is treated with standard medical therapy for heart failure in the absence of other contraindications [110].

Prognosis and Surveillance

The prognosis of LGMD is variable, and even though sudden cardiac death has not been implicated in any forms of LGMD, cardiac surveillance is recommended in these patients.

- A 2-year cardiac follow-up is recommended in asymptomatic patients and annual workup is done for patients with positive cardiac findings, using an ECG and ECHO testing.
- In LGMD1B patients, an additional Holter monitoring is also recommended [37].

Cardiac Management in LGMD



Myotonic Dystrophy

Disease Subtypes

Myotonic dystrophy (DM) is one of the most prevalent adult form of progressive multisystem muscular dystrophy that has two main subtypes that has been described [111]:

– Myotonic dystrophy type 1 (DM1)
– Myotonic dystrophy type 2 (DM2)

Inheritance

The two forms of DM are inherited in an autosomal dominant fashion and is a trinucleotide repeat disease. DM1 is caused by a trinucleotide repeat (CTG) expansion in the myotonic dystrophy protein kinase (DMPK) gene at the 19q13 locus [112]. DM2 results from CCTG repeat in the intron 1 of cellular nucleic acid-binding protein (CNBP/zinc finger protein 9) gene at the 3q21 locus [113].

Pathophysiology

The pathophysiological mechanism explained is acquiring a repeat mutation that results in abnormal RNA production which further results in splicing defects in RNA transcripts that encode for voltage-gated sodium channels, ryanodine receptors, cardiac troponin T, calcium ATPase in sarcoplasmic reticulum, which all together contribute to the cardiac phenotype [70]. These patients also exhibit a phenomenon called anticipation in which an increase in the number of repeats is noted in their offspring. This means that the children of affected individuals develop more severe disease at an early age than their parent [114].

Epidemiology

Myotonic dystrophy has an estimated worldwide prevalence of approximately 1 in 8000 individuals and DM1 has a prevalence of 3–15 per 100,000 individuals. The frequency of the different subtypes varies depending on various ethnic classes though fewer studies are available on DM2 type [115, 116]. The age of onset of DM1 is variable due to anticipation and that of DM2 is around the third to fourth decade of life [70].

Clinical features of myotonic dystrophy

DM type	Clinical features
DM type 1	DM1 has a congenital form and a classic adult-onset form. In adults, there is progressive muscle weakness involving the head, neck, and then limb muscles [117]. The patients also tend to develop myotonia involving the face, jaw, and tongue which improves on contraction [118]. Other manifestations include daytime sleepiness and respiratory failure; cognitive and intellectual deficits; endocrine dysfunction; and gastrointestinal dysfunction [111]
DM type 2	DM2 patients have more mild proximal muscle weakness and compared to DM1 these patients have more pain, stiffness, and fatigue [119]. These patients have other features like cataracts and endocrine dysfunction [111]

Cardiac involvement in myotonic dystrophy

DM type	Cardiac features
DM type 1	The most common cardiac disease noted in DM1 is progressive conduction defects. They also have an increased risk of sudden cardiac death as a result of a fatal arrhythmias or a progressive left ventricular dysfunction. These patients can develop bradycardia and when the atrioventricular block is severe can result in asystole. Tachyarrhythmias including atrial and ventricular arrhythmias can occur in these patients, of which atrial arrhythmias are more common [120]. Though cardiomyopathy is rare in these patients, left ventricular dysfunction can occur in approximately 10% of patients which can eventually lead to heart failure [121]. Other cardiac manifestations include impaired cardiac relaxation, mitral valve prolapse [122]
DM type 2	DM2 patients can develop arrhythmias and heart failure; however, it was more common to see left ventricular systolic dysfunction in these patients [123]. Studies have also shown that in comparison to DM1 these patients have an increased risk of sudden cardiac death [124]

Diagnostic testing in myotonic dystrophy

Diagnostic test	Description
EMG	DM can have specific features on EMG which shows increasing and decreasing bursts of potentials in both the subtypes. However, these need not be seen in all patients and finding can be non-diagnostic [125]
ECG	ECG and Holter monitoring help determine any changes in cardiac conduction. Changes like prolonged PR interval, QRS widening, and varying degrees of atrioventricular block and tachyarrhythmias can be detected on electrophysiological studies. Since these patients have an increased chance of sudden cardiac death, follow-up is essential [126]
ECHO	ECHO helps assessment of chamber size, wall motion abnormalities, and cardiac dysfunction [70]
Cardiac MRI	MRI helps to assess the extent of fibrofatty infiltration in the myocardium in DM patients [127]
Muscle biopsy	Biopsy features include varying size of fibers, perpendicularly arranged myofibril bundles [125]
Cardiac muscle biopsy	Biopsy shows loss of cardiomyocytes, cell hypertrophy, and fibrofatty infiltration. Due to the increased predilection for the conduction system of the heart, arrhythmias can develop in the early stages of the disease [124]
Genetic testing	This is the gold standard for diagnosis, and the technique of PCR helps identify repeats <100 and larger repeats are determined by Southern blotting. Triplet-primed PCR, though considered more sensitive, does not give the number of repeats [128]

Treatment

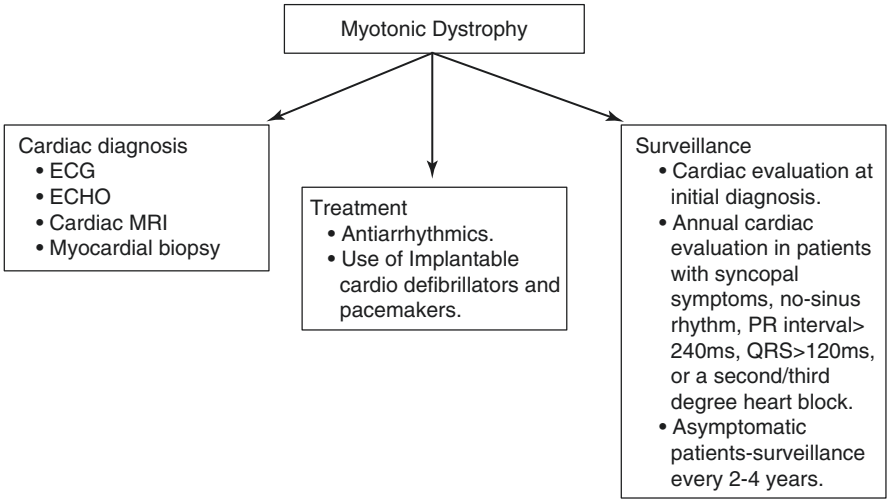
No current treatment is available that changes the course of the disease in either subtypes. The goal of management in DM is to preserve function, provide symptomatic treatment, and prevent complications. Treatment of hypersomnolence can be treated with stimulants, anabolic steroids can help with muscle wasting, and myotonia can be improved with various antiarrhythmics and anticonvulsants [120]. Cardiac management includes use of pacemaker and implantable defibrillator which

can be lifesaving. Patient should be educated about episodes of lightheadedness, palpitation, or even syncope as it requires immediate cardiac evaluation [125]. Symptomatic patients are considered to undergo an electrophysiology study like Holter monitor or loop recorder before they get an implantable device [37].

Prognosis and Surveillance

Cardiac arrhythmias are one of the most common causes of death in almost one-fourth of DM1 patients [126]. DM2 has a comparatively favorable clinical outcome with a greater life expectancy due to the lack of anticipation or any congenital form [115]. Similar surveillance guidelines are applied for either forms of DMs. Patients who are diagnosed with DM is recommended to undergo cardiac evaluation with ECG, ECHO, and Holter monitoring even when they are asymptomatic. Patients who have syncopal symptoms, no-sinus rhythm, PR interval >240 ms, QRS >120 ms, or a second/third degree heart block is recommended to undergo annual cardiac testing. For asymptomatic individuals, cardiac surveillance is recommended every 2–4 years [37].

Cardiac Management in Myotonic Dystrophy



Barth Syndrome

Definition

Barth syndrome (BTHS) is an inherited disorder characterized by skeletal muscle weakness, cardiomyopathy, neutropenia, lactic acidosis, and organic aciduria [129].

Inheritance

BTHS is a disease inherited in an X-linked recessive disorder caused by mutation in the TAZ gene at Xq28 locus which encodes for tafazzin [130].

Pathophysiology

Tafazzin is a phospholipid transcyclase that plays a pivotal role in cardiolipin remodeling which in turn has a key role in maintaining mitochondrial structure and mitochondrial apoptosis [131]. This affects tissues like the heart muscle that consumes high-energy for proper functioning.

Epidemiology

The exact incidence of BTHS is not known, but according to the data collected by the Barth syndrome foundation registry, the prevalence was estimated as 1 in 300,000–400,000 live births [132]. The numbers are considered as high as 1/140,000 live births due to the underdiagnosis of the disease condition [133]. Barth syndrome is more commonly seen to occur among babies and children [135].

Clinical Features

BTHS has non-cardiac manifestations that include proximal skeletal myopathy; dysmorphic facial features; developmental and learning disabilities; metabolic and endocrine abnormalities including exercise-induced lactic acidosis, increased urinary excretion of 3-methylglutaconic acid (MGCA), delayed puberty, growth delay; neutropenia; and recurrent infections [134].

Cardiac Involvement

Cardiac disease is a common clinical manifestation of BTHS of which >70% of individuals have evidence of cardiomyopathy within the first year of life [134]. Dilated cardiomyopathy is the common type and the left ventricle is the most affected, though all four chambers are affected [136]. Patients can demonstrate endocardial fibroelastosis, a mixed dilated-hypertrophic cardiomyopathy, or left-ventricular non-compaction as well [137]. These patients can also develop cardiac conduction defects which occur in correlation to other associated conditions like heart failure, syncope, acidosis, or recurrent infections [138]. The cardiac dysfunction occurs in early childhood with improvement over the years, followed by a progressive decline in cardiac function in a group of affected individuals [139]. Sudden cardiac death may occur in these patients due to fatal ventricular arrhythmias and those with orthostatic syncopal symptoms, and a positive family history of sudden cardiac death is considered to be at a high risk [140].

Diagnosis

BTHS has been diagnosed based on the combination of cardioskeletal manifestations, neutropenia, and organic aciduria; however, due to the varying clinical manifestations, various diagnostic tests are being used to aid diagnosis.

Diagnostic testing in Barth syndrome

Diagnostic test	Description
Blood tests	Neutropenia with levels ranging between 500 and 1500 neutrophils/mL helps assess the risk and severity of infections Increased plasma levels of 3-MGCA [76] *Monolysocardiolipin/cardiolipin (MLCL: L4-CL) ratio testing* *Advantages are that it is aids fast diagnosis and has 100% sensitivity and specificity* *Disadvantage is that only few centers are available worldwide that perform the test* *If the test is abnormal, it can be followed by genetic testing for confirmation* [141]
Urine tests	Mild to moderate increase in urinary excretion of 3-MGCA which could be missed by the diagnostic laboratories [76]
ECG	Initial changes on ECG may include flattening of ST segment, T-wave inversions, and prolonged corrected QT interval [142]. Patients can show various cardiac arrhythmias on ECG, and ventricular tachyarrhythmias may result in sudden cardiac death [37]
ECHO	ECHO is used to look for cardiomyopathy and assess for any cardiac dysfunction in these patients. Left-ventricular non-compaction can be seen at the left ventricular wall as a spongy structure, called as spongiform cardiomyopathy [143]
Genetic testing	Genetic testing is confirmatory for all patients as well as helps identify family members to aid genetic counseling [129]

Treatment

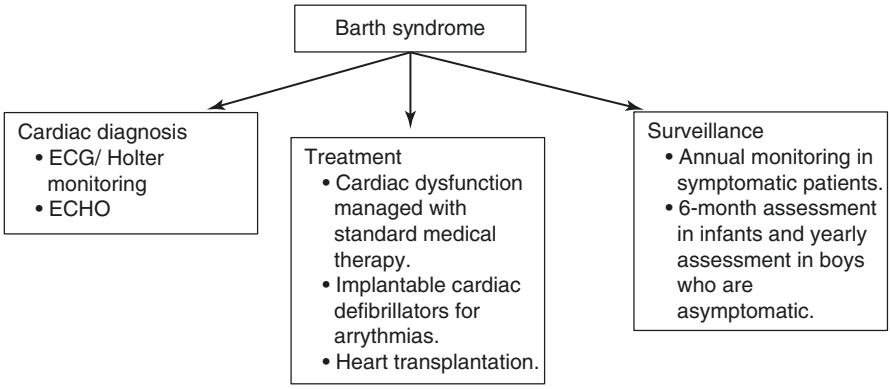
A complete cardiac evaluation is mandatory at the time of diagnosis by a pediatric cardiologist. The cardiomyopathy and associated cardiac dysfunction can be managed by standard medical therapy though these patients may require advanced therapies including cardiac transplantation [129]. Arrhythmias can be a major cause of mortality, and the risk increases in the presence of cardiac dysfunction or metabolic acidosis, thereby increasing the risk of sudden cardiac death. The use of implantable cardiac defibrillators may help prevent the occurrence of this unfortunate event [131]. Heart transplantation is considered in patients after taking into consideration the post-surgical infections because of the neutropenia, and studies have shown a good prognosis in those who survive the first 5 years post-transplantation [144]. The proper management of heart failure with prevention of infections has shown to improve patient survival without the need for a heart transplant [145].

Prognosis and Surveillance

Mortality rates of BTHS patients are considered to be high in the first few years of life that occur either from severe heart failure, fatal arrhythmias, or overwhelming infections.

- Annual assessment in the form of cardiac examination, ECG, ECHO, and Holter monitoring is recommended in all symptomatic patients.
- Annual assessment in boys and 6-month assessment in infants is recommended in asymptomatic individuals [37].

Cardiac Management in Barth Syndrome



Congenital Myopathies

Disease Subtypes

Congenital myopathies are a group of genetic disorders characterized by slowly progressive hypotonia and muscle weakness beginning from birth [146]. They are classified based on the muscle biopsy findings and the types of congenital myopathies include:

- Central core disease
- Nemaline myopathy
- Multiminicore disease
- Centronuclear myopathy
- Congenital fiber type disproportion
- Myosin storage myopathy

Inheritance

Congenital myopathies have an autosomal dominant or recessive form of disease, and this includes the following [147]:

Genetic testing in congenital myopathies

Subtype	Inheritance	Gene locus	Gene product
Central core myopathy	AD/AR	19q13.2	Ryanodine receptor
Nemaline myopathy	AR/AD	1q21, 2q21-q22, 1q42.13, 19q13.4	α-Tropomyosin, nebulin, skeletal muscle α-actin, troponin T
Multiminicore myopathy	AR	19q13.2, 1p36.13	Ryanodine receptor, selenoprotein N1
Centronuclear myopathy	AD/AR	19p13.2, 2q14, 2q31	Dynamin 2, bridging integrator 1, titin
Congenital fiber type disproportion	AR/AD	1q21.2, 19q13.2, 1q42.13	α-Tropomyosin, ryanodine receptor, skeletal muscle α-actin
Myosin storage myopathy	AD	14q12	β-Myosin heavy chain (MHC-β)

Pathophysiology

The affected genes in congenital myopathies form protein products that are components of the sarcomere and are involved in calcium signaling. When the functioning protein is defective, it results in ineffective muscle contraction [148].

Epidemiology

The overall prevalence of congenital myopathies is approximately 1 in 26,000–28,000 individuals of which the ryanodine receptor mutations are the most common form with an approximate prevalence of 1 in 90,000 individuals [149].

Clinical Features

Patients with congenital myopathies have a broad spectrum of severity and in general present with muscle weakness that begins at birth and becomes evident in the first year of life [150]. Patients can have generalized hypotonia, hyporeflexia, proximal muscle weakness, reduced bulk, facial muscle weakness without ptosis, respiratory, and bulbar muscle weakness [151].

Cardiac Involvement

Cardiac disease is an uncommon occurrence in congenital myopathies. It can occur in the form of cardiomyopathy, arrhythmias, heart failure, or sudden cardiac death in patients with nemaline myopathy [152]. Cardiomyopathy, right ventricular failure, and rarely mitral valve prolapse may occur in patients with multiminicore disease [153]. Cardiomyopathy associated with gene mutation encoding for titin has also been reported [154]. MHC-β is a protein that is primarily expressed within the heart and type 1 muscle fibers, and gene mutations can clinically present with either HCM or DCM [155].

Diagnosis

Diagnosing congenital myopathies is based on the clinical findings and muscle biopsy combined, and there are very few data available for cardiac involvement in these group of disorders.

Diagnostic testing in congenital myopathy

Diagnostic test	Description
CK levels/ EMG	These tests are nonspecific as serum CK levels and EMG are generally normal in these patients [146]
ECG/ECHO	ECG can be used for the detection of arrhythmias and ECHO to detect cardiomyopathy and consequent cardiac dysfunction. Holter monitoring can also be performed in these patients for detection of fatal arrhythmias
Muscle biopsy	Nemaline myopathy – small rod-like inclusions within the muscle fibers Central core myopathy – individual rounded core-like structures that are centrally located within the muscle cells Multiminicore myopathy – multiple core-like structures that are seen diffusely Centronuclear myopathy – presence of nuclei at the exact center of the muscle cells Congenital fiber type disproportion – type 1 muscle fibers are found to be smaller than type 2 fibers [146]
Cardiac biopsy	Nemaline myopathy – rod-like inclusions are seen within cardiac muscle fibers, though it is non-uniform Congenital fiber type disproportion – myocardial atrophy, degeneration, and increase in nuclei was seen in the myocardial cells in patients with [156]

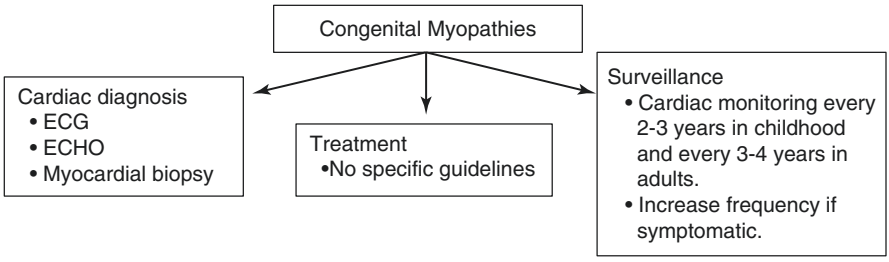
Treatment

There is no given set of treatment guidelines due to the rare occurrence cardiac disease in congenital myopathies. However, since heart disease can occur in these patients, cardiac evaluation at the time of initial diagnosis may be helpful [37].

Surveillance

Though cardiac disease is of rare occurrence, cardiac evaluation is advised in patients with congenital myopathies. A complete cardiac examination, ECG, and ECHO studies every 2–3 years during childhood and every 3–4 years in adults can be performed. The frequency of surveillance may be increased if these patients become symptomatic at any time during the course of the disease [146].

Cardiac Management in Congenital Myopathies



Myofibrillar Myopathies

Disease Subtypes

Myofibrillar myopathies (MFM) are genotypically and phenotypically distinct group of hereditary disorders characterized by the presence of protein aggregates and myofibrillar disintegration on muscle histopathology [157].

Inheritance

The inheritance pattern for various MFM subtypes is as mentioned below [76, 158]:

Genetic testing in myofibrillar myopathy

Subtype	Inheritance	Gene locus	Gene product
Desmin-related MFM	AD/AR	2q35	Desmin
Myotilin-related MFM	AD/AR	5q31.2	Myotilin
ZASP/LDB3-related MFM	AD	10q23.2	LIM domain binding protein 3 (LDB-3)
α-B crystallinopathy	AD/AR	11q23.1	α-B crystallin (CRYAB)
Filamin C-related MFM	AD	7q32.1	Filamin C gamma
BAG-3 related MFM	De novo	10q26.11	BCL2-associated athanogene 3 (BAG-3)
FHL-1 related MFM	XLR	Xq26	Four-and-a-half LIM domains 1 (FHL-1)

Pathophysiology

The genes that are mutated in MFM encodes for proteins that are a part of or have an association with the Z-disc that plays a pivotal role in maintaining the structural integrity of the muscle sarcomere [159].

Epidemiology

Since a genetic cause can be identified only in half of the MFM cases, it is indicative that there are more genes yet to be known that can be associated with affected patients and hence a definitive prevalence rate is still not available [160].

Clinical Features

The presence of slowly progressive muscle weakness beginning in the lower limbs, spreading to upper extremities, trunk, face, and eventually affecting the respiratory muscles is seen in these patients. The involvement of proximal muscles indicates CRYAB or filamin C-related MFM, while distal involvement is seen with desmin, ZASP, and myotilin-related MFM [161].

Cardiac Involvement

Cardiac disease in the form of cardiomyopathy affects almost one-third of patients affected with MFM [162]. The cardiac manifestations seen in these conditions are as below [76]:

Cardiac manifestations in myofibrillar myopathy

Subtype	Cardiac manifestations
Desmin-related MFM	Restrictive cardiomyopathy (RCM); atrioventricular block
Myotilin-related MFM	Non-specified cardiomyopathy
ZASP/LDB3-related MFM	Dilated cardiomyopathy, though it is uncommon
α-B crystallinopathy	RCM; HCM
Filamin C-related MFM	RCM, late onset arrhythmias
BAG-3-related MFM	RCM; HCM; left ventricular noncompaction
FHL-1-related MFM	RCM; LV hypertrophy with atrial dilation

Diagnosis

The diagnosis of MFM can be made on clinical manifestation and histological findings, however genetic testing is required to differentiate the various subtypes of the disease.

Diagnostic testing in myofibrillar myopathy

Diagnostic test	Description
CK levels	A mild to moderate elevation in serum CK is noted in affected patients [157]
EMG	Myopathic and neurogenic features may be seen with abnormal electrical irritability. Nerve conduction study abnormality can be seen in about 20% of MFM patients [160]
Muscle/cardiac biopsy	Both skeletal and cardiac muscle biopsy show accumulation of protein aggregates within the sarcoplasm with myofibrillar disintegration and the presence of vacuoles at the level of the Z-disks [162]
ECG/ECHO	ECG and Holter monitoring can be used for detection of arrhythmias and ECHO to detect various forms of cardiomyopathy and consequent cardiac dysfunction

(continued)

(continued)

Diagnostic test	Description
Cardiac MRI	MRI can detect myocardial fibrosis and cardiac dysfunction earlier than an ECHO; however, no current clinical data suggesting its use in MFM is available
Genetic testing	Genetic testing helps to genotypically differentiate the various forms of MFM, as well as guide prenatal diagnosis and genetic counseling in affected individuals

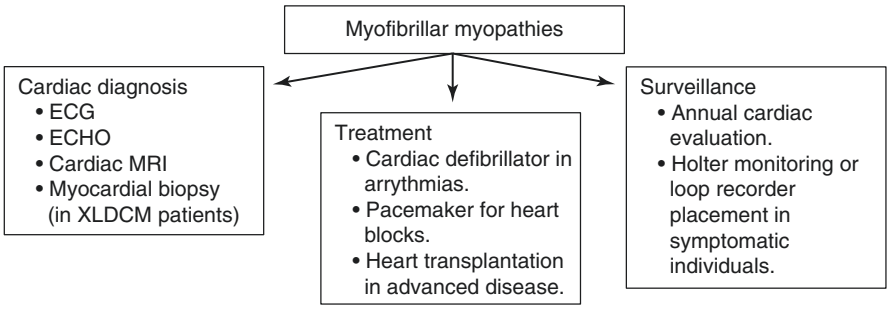
Treatment

MFM patients who develop cardiac conduction defects should undergo pacemaker insertion and those with uncontrolled arrhythmias should have implantable cardiodefibrillator placed [160]. Although heart transplantation can be limited in patients with severe systemic disease, it is considered the ultimate treatment option for those who develop end-stage cardiac disease [76].

Prognosis and Surveillance

Cardiomyopathy can occur in about 15–30% of MFM patients; hence, annual cardiac evaluation with a complete cardiac examination, ECG, and ECHO studies is recommended [160]. Patients with symptomatic cardiac disease in MFM should undergo Holter monitoring or placement of a loop recorder [37].

Cardiac Management in Myofibrillar Myopathies



Conclusion

Over the past several decades, the multidisciplinary approach and treatment advances have been remarkable aiding in the survival of patients with NMDs as well as improving the quality of life. However, cardiac involvement is a part of these diseases that require further improvements as they can be a major form of morbidity and mortality in these patients. This shows the requirement for comprehensive care for the diagnostic evaluation, medical management, and therapeutic interventions in NMD patients with cardiac disease. The various cardiac manifestations in the discussed NMDs are summarized in Table 4.7.

Table 4.7 Cardiac manifestations in various neuromuscular diseases

Disease	Subtype	Cardiomyopathy	AVB	Arrhythmias
Dystrophinopathy	DMD	Common (DCM)	Rare	Rare
	BMD	Common (DCM)	Rare	Rare
	XLDCM	Common (DCM)	–	–
	MC	Common (DCM)	–	–
EDMD	Emerin related	Rare (DCM)	Common	Common
	FHL1 related	Rare (HCM)	Common	Common
	LMNA related (AD)	Rare (DCM)	Common	Common
	LMNA related (AR)	Rare (DCM)	Common	Common
FSHD	–	Rare	Common	Rare
LGMD	LGMD 1B	Common (DCM)	Common	Common
	LGMD 2C	Common (DCM)	Rare	Rare
	LGMD 2D	Common (DCM)	Rare	Rare
	LGMD 2E	Common (DCM)	Common	Common
	LGMD 2F	Rare	Rare	Rare
	LGMD 2I	Common (DCM)	Rare	Rare
DM	DM1	Occasional (DCM, HCM)	Common	Common
	DM2	Rare	Rare	Rare
Barth syndrome	–	Common (DCM, HCM, LVNC)	Occasional	–
Friedreich ataxia	–	Common (HCM)	Common	Rare
Congenital myopathies	Central core myopathy	–	–	–
	Nemaline myopathy	Occasional (DCM, HCM)	Rare	Rare
	Multiminicore myopathy	Rare (HCM, RCM)	–	–
	Centronuclear myopathy	Rare (DCM)	Rare	Rare
	Congenital fiber type disproportion	Rare (DCM)	–	–
	Myosin storage myopathy	Common (HCM, DCM)	–	–
MFM	Desmin related	Common (RCM)	Rare	–
	Myotilin related	Unspecified	–	–
	ZASP/LDB3 related	Uncommon (DCM)	–	–
	α-B crystallinopathy	Uncommon (RCM, HCM)	–	–
	Filamin C related	Uncommon (RCM)	–	–
	BAG-3 related	Occasional (DCM, HCM, LVNC)	–	–
	FHL1 related	Uncommon (RCM)	–	–

Abbreviations: *DMD* Duchenne muscular dystrophy, *BMD* Becker muscular dystrophy, *XLDCM* X-linked dilated cardiomyopathy, *MC* Manifesting carriers of dystrophin gene mutation, *EDMD* Emery–Dreifuss muscular dystrophy, *FSHD* Facioscapulohumeral muscular dystrophy, *LGMD* Limb-girdle muscular dystrophy, *DM* Myotonic dystrophy, *MFM* Myofibrillar myopathies, *DCM* Dilated cardiomyopathy, *HCM* Hypertrophic cardiomyopathy, *RCM* Restrictive cardiomyopathy, *LVNC* Left ventricular noncompaction, *AVB* Atrioventricular block

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Neuromuscular Emergencies in the Neuroscience Intensive Care Unit

5

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Guillian-Barre Syndrome (GBS)

- AKA acute inflammatory demyelinating polyradiculoneuropathy (AIDP).
- It is also called as immune-mediated polyneuropathies.

Introduction

- Most common cause of monophasic acute or subacute generalized paralysis [1, 4].
- Affects children and adults of all ages and both sexes [2].
- Incidence: 0.4–3.25cases/100,000/year [3].
- Weakness usually follows a nonspecific viral infection (for example GI or upper respiratory infection) by about 10 days.
- Two-third of the patient's given history of antecedent respiratory or GI infection.
- *Campylobacter jejuni* is a most frequent identifiable preceded infection (~30% of patients). Others are CMV (~10%), EBV, influenza, mycoplasma, and HIV. Bone marrow transplant, trauma, surgery, and immunization also are shown to be triggers.

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Symptoms

Motor Symptoms

- Major clinical manifestation of GBS
- Symmetrical weakness (however asymmetry seen in 9% of the patients)
- Ascending weakness (however may begin in arms or facial muscles in about 10% patients)
- The weakness progresses and in about 5% of the patient to total motor paralysis with respiratory failure within few days
- Severe respiratory muscle weakness in about 10–30% patients requiring mechanical ventilator
- More than 50% patients have facial nerve palsy
- Up to 50% patients may have oropharyngeal weakness
- Absent deep tendon reflexes (in 90% of patients)

Sensory Symptoms

- Paresthesia of hands and feet are very common (~80%, often first symptom), however mild symptoms
- Back pain and extremity pain are very common/may be presenting feature during the acute phase by two third of the patients with all form of GBS

Autonomic Symptoms

- Dysautonomia present up to 70% of patients.
- MC autonomic features are diarrhea/constipation (16%), hyponatremia (15%), bradycardia (5%), urinary retention (4%), tachycardia (3%), reversible cardiomyopathy (1%), and Horner syndrome (1%).
- Dysautonomia is MCC of sudden death in GBS patients.

Clinical Course

In the absence of disease-modifying agents, GBS progress over 2 weeks, reaches nadir in 4 weeks, and then recovers function over several weeks to months. If the disease progression is for more than 8 weeks, then at this time it is called chronic inflammatory demyelinating polyradiculoneuropathy.

Pathogenesis [7]

- Most likely mechanism of GBS is *immune-mediated response* to preceding infection which also cross-reacts with a peripheral nerve aka *"molecular mimicry"* resulting in multifocal inflammatory demyelination. Both cellular and humoral immune response played major role in immune-mediated response.
- Immune response as directed toward myelin or axon of the peripheral nerves usually starts at the level of nerve roots. Earliest changes are frequently seen at the nodes of Ranvier.

- Invasion by activated T cells is followed by macrophage-mediated demyelination with evidence of complement and immunoglobulin deposition on myelin and Schwann cells.

GBS Variants

- *Anti-ganglioside GQ 1b antibody syndromes:*
  - *Miller Fisher syndrome*
    MC variant: [8] seen in up to 10% GBS cases in the United States.
    Typical presentation: Ophthalmoplegia + ataxia + areflexia.
    One-fourth of the patient may have some extremity weakness.
    MFS may present with descending paralysis.
    Anti-ganglioside GQ 1b present in ~90% of patient with MFS.
    Presence of antibodies strongly linked with involvement of the oculomotor nerve.
    Atypical forms of Miller Fisher syndrome is also reported like ophthalmoplegia without ataxia, without areflexia, or both. Dilated fixed pupil is also reported to be a variant of Miller Fisher syndrome.
    Diagnosis:
    (a) +ve IgG anti-GQ 1b antibodies.
    (b) EMG/NCV of MFS reveals reduced or absent sensory response with normal conduction velocity. Motor conduction abnormalities can be seen when there is an associated weakness.
  - *Bickerstaff encephalitis:*
    Rare variant
    Features of Miller Fisher syndrome (except hyporeflexia) + encephalopathy
    NOTE: Presents have hyperreflexia instead of hyporeflexia, which is a usual manifestation of GBS
    Associated with anti-ganglioside GQ 1b antibody
    Improved by IVIG/PLEX
  - *Pharyngeal-cervical-brachial weakness*:
    Possible localized form of axonal GBS.
    Some patients have IgG autoantibodies to GQ1b, *GT1a* and GD1a.
    As name suggests, oropharyngeal, cervical, and shoulder muscles are involved. Facial muscles may involve sometimes.
    Rest of the strength of upper or lower limb are usually preserved.
  - *Pure sensory GBS:*
    Prominent symptom is sensory ataxia and absent reflexes
    Involves large sensory and proprioceptive fibers
    Associated with GQ 1B antibodies
  - *Acute bulbar palsy +/− ophthalmoplegia, ataxia and facial palsy* is also believed to be a variant of GBS.
    Associated antibodies-IgG anti-GT 1a antibodies >IgG anti-GQ 1b antibodies.
    Neck and limb weakness are absent.

- *Acute motor axonal neuropathy and acute motor and sensory neuropathy* are estimated to be seen up to 5–10% of GBS cases in the United States.
  - *Acute motor axonal neuropathy (AMAN):*
    Acute axonal form of GBS.
    Antibody to *gangliosides G M1*, GD 1a, GalNac-GD1a, and GD1b.
    Strongly related with *Campylobacter*.
    Common in Asia, particularly in young people.
    Striking features: preserved deep tendon reflexes, sensory nerves are not involved. Rapid progression of disease, however similar prognosis as GBS.
    EMG/NCV shows decreased motor amplitudes without sensory nerve involvement (normal conduction velocities and distal latencies) or evidence of peripheral nerve demyelination (no temporal dispersion). Conduction block may or may not be present in AMAN.
  - *Acute motor and sensory axonal neuropathy (AMSAN):*
    AMSAN more severe than AMAN (has both sensory and motor fibers are affected with marked axonal degeneration)
    EMG/NCV: Shows severely reduced or absent axonal amplitudes, conduction velocity, increased latencies with temporal dispersion
- *Other GBS variants:*
  - *Acute pandysautonomia:*
    Prominent dysautonomia +/− weakness. Symptoms include diarrhea or vomiting, abdominal pain, ileus, orthostatic hypotension, urinary retention, pupillary involvement, tachycardia or bradycardia, salivation, lacrimation, decreased sweating. This is associated with decreased or absent reflexes.
    Treatment with IVIG.
  - *Facial diplegia with paresthesia* and *sixth nerve palsy with paresthesia:*
    Also reported to be a variant

Laboratory Test [12]

- CBC: Rule out concurrent infection.
- CMP: normovolemic hyponatremia (2/2 SIADH) --> obtain plasma and urine osmolality.
- Liver enzymes: mild increase (unknown reason) can be seen in one-third of patients (obtain hepatitis panel).
- ESR: Mildly elevated (indicative of recent infection)
- Creatine kinase: may slightly increase.
- UA: Transient proteinuria may be seen.
- Demyelination-related testing: anti-GM1, anti-GD1, MAG, and anti-GQ1b.
- Stool for PCR: For *C. jejuni*.
- ABG: If suspecting respiratory failure.
- CXR: if shows atelectasis then suspect possible dysphagia. Infiltrate or pleural effusion my also predicts early need of intubation. May indicate early NSICU admission.

- Spirometry: NIF and VC: predict intubation.
- EKG: May indicate dysautonomia. Prolongation of RR Interval is related with impending fatal dysautonomia (??).
- CT Head: If needed before LP.
- LP: CSF for cyto-albumin dissociation. Elevation in CSF protein may not absent up to 1 week after onset of symptoms. GBS associated with HIV infection features a CSF leukocytosis.
- MRI spine: Shows enhancement of anterior nerve roots (95% of cases).
- EMG/NCV: Earliest changes can be seen as early as Day 5 which includes absent H reflex, abnormal F wave, and abnormal upper extremity SNAP combined with a sural sparing are characteristic of early GBS.

Diagnosis [12]

- Electrodiagnostic studies:
- NCV:
  - Nerve conduction studies shows slow conduction velocity, abnormal upper extremity SNAP, or absent H responses.
  - In some patients, in first few days of weakness, nerve conduction studies can show sural sparing pattern (i.e., normal sural nerve sensory response, but median and ulnar sensory responses are affected).
  - Sural nerve sparing pattern have high specificity and low-moderate sensitivity for AIDP.
- EMG:
  - Hallmark of GBS is conduction slowing with conduction blocks.
  - Earliest change is prolonged or absent F waves and absent ankle reflexes.
  - Later conduction block, temporal dispersion with increased distal latencies of motor response follows.
  - Slowing of nerve conduction velocities usually seen in third or fourth week.
- Needle EMG: will show reduced recruitment of the affected muscles.
- Absent H reflex, abnormal F wave, and abnormal upper extremity SNAP combined with a normal sural SNAP are characteristic of early GBS.

Recommendation for ICU admission [11, 13]

- *Rapid disease progression to severe weakness (<7 days)*
  - Increasing generalized weakness or easy fatigability.
  - Significant weakness of neck muscles.
  - This is associated with poor prognosis.
- *Impending Respiratory failure:*
  - Dysphonia
  - Dysphagia
  - Dyspnea on exertion and at rest
  - Use of accessory muscles

  - Rapid shallow breathing
  - Involvement of the respiratory muscles
  - Abdominal paradox
  - Orthopnea
  - Nocturnal desaturation
  - Weak cough (predicts respiratory muscles weakness)
  - Cough after swallowing
  - Staccato speech
  - Single breath count: see below
  - PFT's: FVC <40 ml/kg; NIF <−40 cmH2O; Decline of FVC or NIF >30% in last 24 hrs
- *Involvement of bulbar and/or facial muscles:*
  - Failed swallow evaluation
  - CXR showing infiltrates, atelectasis, or pleural effusion. (Indirect evidence of weak swallowing and respiratory muscle weakness)
  - Worsening dysphagia
  - Facial weakness
  - Weak palatal elevation
  - Weak cough and gag
- *Autonomic instability* [6]*:*
  - EKG: tachycardia, bradycardia, prolong R-R interval, ST depression, Prolong qTc interval, and T wave inversion.
  - Labile blood pressure.
  - Profound sensitive to sedative medications.
  - Profound bradycardia may require temporary pacemaker.
  - These people are prone to cardiac arrhythmias secondary to endotracheal suctioning and thus nurses and respiratory therapists should be warned about the situation.
- *Medical complication:*
  - Addressing multiple life-threatening issues (ex-PE, DVT, MI, etc.)
- *Others*
  - May require frequent neurological examination. Vital signs check q1-q2 h.
  - Intensive nursing care
    Time of onset to admission <7 days
    PLEX planned, requiring frequent examination

ICU Management

- *Assessment of intubation* [14]*: High risk for future intubation/impending respiratory failure are:*
  - Figure 5.1 outlines the overall approach to respiratory failure in the patient with Guillain-Barré syndrome.
- *ABG:*
  - PaO2 <70 on room air
  - PaCO2 >45 or significant increase

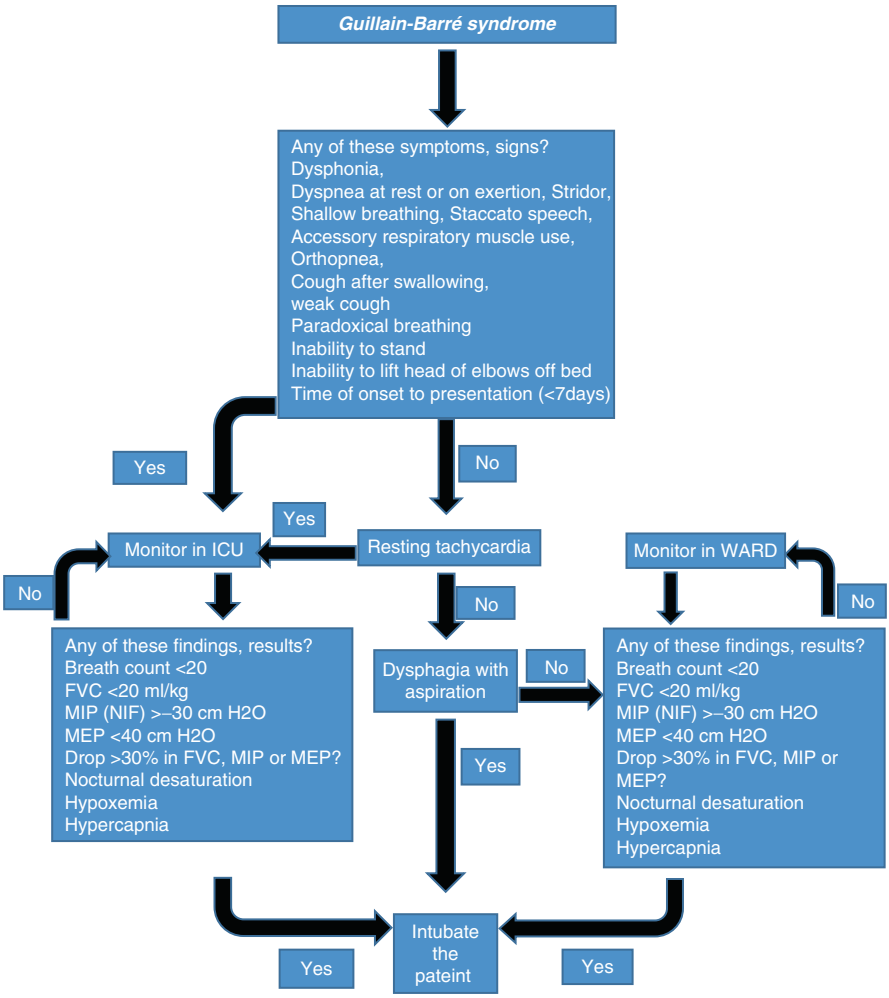

Fig. 5.1 Approach to respiratory failure in the patient with Guillain-Barré syndrome. (Adapted from Sleep Disorder in Neuromuscular Disorders a Clinical Guide by Raghav Govindarajan)

- *PFT*
  - Frequent respiratory evaluation: q 2–4 h while awake; q 4–6 h when asleep
- *Rule of 20–30–40-50.:*
  - Intubate if anyone is present
  - Forced vital capacity <20 mL/kg or
  - Maximal inspiratory pressure (NIF) <−30 cm of H2O or
  - Maximal expiratory pressure <40 cm H2O
  - Decrease of anyone of above >30–50% in 24 hrs
- *Single breath test:*
  - Count as high as possible in one breath
  - Able to count >25 in single breath = FVC ~>2 L

  - Able to count >10 in single breath = FVC ~>1 L
  - If there is >25% decrease in FVC when supine suggest significant diaphragmatic weakness
- *Bulbar weakness:*
  - Weak cough and gag
  - Dysphagia
  - Cough after swallowing
  - Severe dysarthria
  - Facial weakness
  - Up to 10–30% patients of GBS requiring mechanical ventilator due to respiratory muscle weakness and will require admission to an ICU
- Earlier intubation related with lower pulmonary complications and to avoid complications associated with emergent intubation. Ventilatory weaning should be considered as a patient's condition improves.
- Few considerations during intubation in the GBS patients:
  - Chronic denervation condition (e.g., GBS), chronic neurologic conditions (e.g., stroke), immobility (e.g., spinal cord injury), and or other long-standing neuromuscular weakness (e.g., ALS, MS, myopathies) lead to upregulation of the Ach-receptors. In these cases, use of depolarizing agents such as succinylcholine increases the risk of life-threatening hyperkalemia and arrhythmia. Hence, succinylcholine is contraindicated in GBS patients. Instead use of the non-depolarizing agents was advocated. However, still dose adjustment with reduced dose is required for non-depolarizing agents to avoid prolonged adverse effects.
  - Glycopyrrolate may be used in GBS patients with autonomic instability (tachy-bradyarrhythmia's).

Predictor of prolonged intubations: [15, 16] and thus require early tracheostomy.

- Widespread fibrillations.
- Absent motor responses.
- Lack of dorsiflexion of feet at ICU admission and at the end of therapy.
- Inability to lift the arm 1 week after the intubation.
- In these patients, consider cuff test or extubation under direct laryngoscopic visualization prior to extubation in cases of prolonged intubations.
- Most GBS patients need trach since mechanical ventilation duration is prolonged.

Weaning criteria

- Strength improving on confrontation testing
- FVC >10 mL/kg or NIF >–20 cmH2O

Extubation criteria

- Vital capacity >15 mL/kg,
- Maximal inspiratory pressure >−30 cm H2O

- Satisfactory oxygenation
- Minimal pressure support
- Minimal secretions
- Passing SBT

Management of GBS [9, 10]

Treatment with disease-modifying agents is most effective if started within 14 days of symptoms onset.

- *Disease-modifying treatment include:*
- *Intravenous Immunoglobulins (IVIG):*
  (a) Dose: 0.4 mg/kg q 1 day × 5 days.
  (b) IVIG is as effective as plasmapheresis.
  (c) IVIG precise mechanism is unknown; however, it is postulated that it may provide anti-idiotypic antibodies, modulating expression and function of Fc receptors, interfering with activation of complement, interfering with production of cytokines, and interfering with activation and effective function of T and B cells.
  (d) Patients with more severe clinical disease may benefit for longer duration of IVIG treatment.
  (e) IVIG is associated with lower complication rate [[60],69].
  (f) *Side effects and contraindications:*
    (i) Anaphylaxis in IgA-deficient patient (ALWAYS CHECK IgA LEVEL).
    (ii) General: Flu like symptoms; nervous system: aseptic meningitis, HA, reversible encephalopathy; cardiovascular: hypertension, chest pain, and thromboembolism. Contraindicated in CHF, and renal insufficiency. Renal: AKI. GI nausea and vomiting.
- *Plasma exchange:*
  (a) Dose: 1 volume every 1–2 days for five exchanges.
  (b) Plasma exchange removed circulating antibodies, complement and soluble biological response modifier. With plasma exchange, there is early improvement in muscle strength and reduced need for mechanical ventilation and better recovery.
  (c) *Side effects and contraindications:* Hypocalcemia, transfusion reaction, hypotension, infection, pneumothorax, and hematoma. Contraindication in septic shock, MI within 6 months, active bleeding, and *marked dysautonomia.*
- *Recommendation of therapy:*
  (a) Plasma exchange is recommended for ambulatory patient who start treatment within 2 weeks of the onset of neuropathic symptoms. Patient improved sooner when treated early.
  (b) Plasma exchange is recommended for nonambulatory patients with GBS who started treatment within 4 weeks of neuropathic symptom onset.
  (c) IVIG is recommended for nonambulatory patients with GBS who started treatment within 2 or possibly 4 weeks on the onset of neuropathic symptoms.

- *Guidelines from the American Academy of neurology have made the following observations:*
  (a) Treatment with plasma exchange or IVIG has fastened the recovery.
  (b) Combining the 2 treatment is not beneficial.
  (c) Steroid treatment is not recommended.
  (d) Beneficial effect of the plasma exchange and IVIG are equivalent.
- *Supportive management:*
  – Autonomic failure
    (a) Prevention:
      (i) Maintain positive fluid balance, as insensible losses are often markedly increased.
      (ii) Monitor for dysrhythmia (predicted by prolonged R-R interval).
    (b) Treatment:
      (i) Labile blood pressure: With transient increases and decreases of normal mean pressure, use short-acting agents.
      (ii) Hypotension – First treat with fluids; second line: pressors; *phenylephrine is pressor of choice*. Note: primary problem is peripheral vasodilation.
      (iii) Hypertension – treat only extremes of blood pressure; consider short-acting peripheral vasodilator agents like *nicardipine or sodium nitroprusside.*
  – Chest physiotherapy
    (a) Chest PT, cough stimulation, etc., particularly if not intubated.
    (b) Remember these people are prone to develop cardiac arrhythmia 2/2 endotracheal suctioning.
    (c) Recruitment maneuvers.
  – Aggressive prophylaxis for DVT and ulcer (very high risk for DVT and moderate risk for ulcer).
  – Nutrition:
    (a) GBS is hypercatabolic state.
    (b) Start tube feeding as soon as possible.
    (c) Early feeding helps to avoid risk of infection and failure to wean from mechanical ventilation.
    (d) Initial replacement: 30-40 kcal/kg non-protein calories +2–2.5 protein/kg.
    (e) Obtain indirect calorimetry.
    (f) Weekly 24-hour urine samples can help calculate nitrogen balance and protein needs.
    (g) Weekly transferrin should be collected instead of albumin if patient is getting PLEX.
  – Psychological support:
    (a) Engage patient in routine activity.
    (b) Reader board for patient who cannot speak.

Prognosis of the Patient on GBS [17]:

- Monophasic syndrome. However, recurrence occurs in up to 5% cases.
- Usually good prognosis with spontaneous recovery which begins in 2–3 weeks of acute presentation.
- Most patients regained full muscular strength without residual weakness.
- Improvement usually follows inverse direction of involvement.
- Tendon reflexes are last to recover.
- Overall mortality: 2.4–6.4%
- Mortality in patients who are mechanically ventilated: 15–30%
- MCCOD is dysautonomia. However, other causes are infection, ARDS, or PE.
- Patients who are on mechanical ventilated will regain ability to walk independently up to 2 year after GBS onset.

Poor Prognostic factors [18]

- Age >60 yr.
- Antecedent h/o *C. jejuni* infection.
- Upper limb paralysis.
- Rapid progression to severe weakness <7 days or (Maximum disability at the time of presentation).
- Axonal variants of GBS usually have slower, delayed, and often incomplete recovery.
- Positive IgG-Anti GM1 antibody.
- CMAP amplitude <20% of normal.
- Intubation (mechanical ventilator support).

Myasthenia Gravis (MG)

Introduction

- "Myasthenia" has a Greek origin, whereas "gravis" is Latin, which is literally means *grave muscle weakness.*
- *Most common disorder* of neuromuscular junction (NMJ).
- Autoimmune disorder causes weakness and fatigability of the skeletal muscles [19].

Epidemiology

- Incidence: 5.3 (1.7–21.3)/million.
- Prevalence: 77.7 (15–179)/million [20]
- Affects any age, however have bimodal distribution in both genders.

- Early peak in second to third decades (females>male).
- Late peak in sixth to eighth decades (males >females) [21].
- Post-partum women are increased risk for clinical onset MG [22].

Etiopathogenesis

- Weakness caused by destruction of acetylcholine receptor (AchR) and/or receptor associated protein (like AchR binding, blocking or modulating protein) by antibody attack or T-cell dependent immunological attack.
  - AChR antibodies are majorly *binding*, followed by *blocking* (10%) and *modulating* (1%) type.
  - Other antibodies which can be seen in MG are anti-MuSK (muscle-specific receptor tyrosine kinase antibodies).
  - Patient with detectable antibodies were called seropositive MG (~90–95%) versus seronegative MG patient in which no antibodies were detected (~5–10% patients).
- ~50% patients with seronegative MG have clustered AChR antibodies (also called low-affinity AChR antibodies), when tested by a specialized cell-based immunofluorescence assay. Other more recent antibodies were also been found to be associated with MG were lipoprotein-related protein 4 (LRP4), cortactin, ryanodine receptor, titin, myosin, alpha actin, actin, rapsyn, and gravin [21, 23].
- All these antibodies ultimately lead to loss of functional acetylcholine receptor (AchR) at the NMJ.
- As of any other autoimmune disease, MG is also associated with other autoimmune disease like hypothyroidism, hyperthyroidism, RA, SLE, etc.
- Up to 75% of the MG patients have thymus involvement. Out of those, ~10–15% of the patients with MG have underlying thymoma, and ~85% patients have thymic hyperplasia.

Clinical Forms of Classical MG

Two clinical forms:

- *Ocular myasthenia.*
  - Purely ocular involvement (levator palpebrae superioris, orbicularis occuli, and oculomotor muscles) without any other weakness
  - ~ 50% patients are seropositive.
  - Two-third patient with ocular myasthenia will develop generalized myasthenia in the future.
  - Of these two-third patients:
    (a) ~78% will developed generalized myasthenia gravis <1 year.
    (b) ~94% will develop generalized myasthenia by 3 years.
- *Generalized myasthenia:*
  - Weakness commonly affects ocular muscles, but it also involves other muscles.
  - ~ 90% patients are seropositive.

Clinical Features of MG

- Hallmark of myasthenia gravis is-fluctuating weakness.
- Persistent activity or repeated activity of the muscle group exhausts its contractile power which further leads to progressive weakness.
- There is a tendency to increase in weakness of muscle as the day progress (d/t repeated use of the muscle) or after exercise.
- The strength of the muscle is restored at rest.
  - *Presenting symptoms:*
    (a) Although myasthenia can produce weakness of any skeletal muscle group, the special vulnerability of certain muscles to be affected in case of myasthenia gravis is very characteristic of myasthenia.
    (b) Muscles which are mainly affected arm those innervated by motor nuclei of the brainstem. These group are ocular (CN-3, 4&6), masticatory (CN-5), facial (CN-7), deglutition (CN9&10), and lingual muscle (CN-12).
    (c) ~ 50% MG patients initially presents with ocular muscles weakness. Involvement of levator palpebrae or extraocular muscles causes ptosis (unilateral or bilateral) and/or binocular diplopia (horizontal or vertical) *without pupillary involvement* as the MC presenting symptom. Half of the patients who initially presented with ocular symptoms will develop generalized myasthenia within 2 years [24].
    (d) ~15% patients initially presented with bulbar symptoms include dysarthria, dysphagia (d/t oropharyngeal muscle weakness), fatigable chewing (e.g., more difficult to eat or after talking), nasal intonation, hypophonic voice, nasal regurgitation (weakness of palatal muscles), or jaw weakness. When jaw weakness (jaw sag) is present at rest, the patients often use their fingers under the jaw to keep the mouth shut. When facial muscles involved patient appears expressionless, natural smile turned into snarl called "myasthenic snarl" [24]
    (e) <5% presents with proximal limb weakness (arms>legs) alone.
  - Other less common presentations include distal limb weakness, isolated respiratory muscle weakness (~1%), and isolated neck weakness (producing dropping head syndrome).
  - In advanced disease: all muscles are weakened including the diaphragmatic, abdominal, intercostal, and external sphincters of bladder and bowel.

Important pertinent negative findings:

- Deep tendon reflexes are preserved even with repeated taps.
- Smooth muscles and cardiac muscles never involve.
- Patients have no sensory symptoms and rarely have of muscle pain.

Clinical Course

- Progression of MG peaks in 2–3 years.
- ~1/2 of the patients who initially presented with ocular symptoms will develop generalized myasthenia within 2 years [25].

- No factors (e.g., IgG-AChR level, decremental response in repetitive nerve stimulation test, or abnormal single-fiber electromyographic studies) can predict which patients with ocular MG will develop generalized MG in future [24].

Precipitating Factors for MG Exacerbation

- MCC is concurrent infection (e.g., respiratory tract infection, aspiration pneumonia).
- Recent surgery (e.g., thymectomy).
- Pregnancy, perimenstrual state.
- Tapering of the immuno-modulating medications.
- Natural course of the disease.
- Drugs that cause precipitation of the myasthenic crisis were categorized in Table 5.1.

Table 5.1 Drugs that worsen or precipitate the myasthenic crisis

Class	Medication
Neuromuscular blocking agents	Botox, Succinylcholine Isoflurane Halothane
Antibiotics	Aminoglycosides, Fluoroquinolones, Macrolides or Tetracycline Chloroquine
Antiepileptic	Gabapentin Phenytoin CBZ Ethosuximide
Glucocorticoids	Dexamethasone Prednisone Methylprednisone
Antiarrhythmic	Beta blockers CCB Lidocaine Procainamide Quinidine
Antipsychotics	Chlorpromazine Prochlorpromazine Lithium
Anti-PD-1 monoclonal antibodies	Pembrolizumab Nivolumab
Other	Magnesium Riluzole Iodinated contrast agent Statins Glatiramer acetate Interferon alpha

Myasthenic Crisis

- Severe form of the MG exacerbation.
- MC reason for admission to ICU.
- Too little acetylcholine leads to worsening generalized weakness, with impending respiratory failure (usually FVC <1 L) requiring mechanical ventilation. Also, be suspicious for myasthenic crisis in an already intubated MG patient in which extubation is delayed for >24 hrs.
- Impending myasthenia crisis: rapid clinical worsening for the MG which will progress to crisis in a short term (days to weeks)
- ~20% of patients with myasthenia gravis experience at least one myasthenic crisis in their lives.
- ~2–3% of annual risk of myasthenic crisis in patients with myasthenia gravis.
- ~13–20% of the MG patients can initially present as myasthenic crisis.
- Usually myasthenic crisis occurs during first few years of the diagnosis, with a median time ranging from 8 to 12 months.
- Current mortality rate, which is greatly reduced in last 5 decades, is 4.5% and is primarily the result of comorbid medical conditions.

Clinical Presentation of Myasthenia Crisis

Most common presentations are:

- Worsening generalized weakness
  - Expressionless face with facial droop
- Worsening bulbar weakness
  - Unable to support head
  - Jaw drop
  - Nasal intonation
  - Absent gag or cough reflex
- Weakness of the respiratory muscles
  - Respiratory distress (may not be obvious use of accessory muscles because of worsening weakness)
  - Rapid and shallow breathing
- Or in combination of above

Cholinergic Crisis (Too Much Acetylcholine)

- Usually seen with dose of >120 mg q 3 hr. of pyridostigmine
- Very rare in low dose of the pyridostigmine
- Important differential for myasthenia crisis
- Common features between the two: both present with generalized weakness with and without respiratory failure

Table 5.2 Some provocative maneuvers for MG

Sustained up-gaze (60–180 seconds)	Look for worsening of ptosis
Manual elevation of the more ptotic lid. "Curtain sign"	Look for worsening ptosis (curtaining) of the contralateral eyelid
Sustained tight closure of the eyelids for "peek sign"	Look for the gradually become apparent white sclera of the eye
Sustained lateral gaze (60 seconds)	Look for fatigable diplopia
Counting aloud (1–50):	Usually person can count up to 50 without difficulty
High-pitched ("eeee") sound for testing laryngeal muscles	Look for laryngeal fatigability
Sustained abduction of the arms (120 sec)	Look for weakness in muscles responsible for abduction
Sustained elevation of leg while lying supine (90 seconds)	Look for weakness or drift

- Differentiating features for cholinergic crisis are DUMBELSS (diarrhea, urinary incontinence, miosis, bradycardia, emesis, lacrimation, salivation, and sweating)

Examination and Workup

Bedside examination: Few of the quick bedside assessment were summarized in Table 5.2.

- *Icepack test*
  - Applying ice over the eyelid for 2 minutes temporarily improves the ptosis.
  - Physiological basis of test: Decrease of temperature transiently increases the availability of the acetylcholine in the synapse due to temporary decreased activity of the acetylcholinesterase. The sensitivity is 82% and specificity is 96%. Can be done in outpatient. Not helpful for extraocular muscle weakness.
- *Tensilon test:* Edrophonium and neostigmine is short-acting acetylcholinesterase inhibitor which will transiently increase acetylcholine in the synapse resulting in improvement of the weakness. The potential side effects of the edrophonium are related to increase of the acetylcholine, such as bradycardia, hypotension, and increased secretion, and hence test should be done while patient is admitted in the hospital. 95% sensitive for generalized MG and 85% sensitive for Ocular MG. Of note, edrophonium is no longer available in the United States.
  - *Remember key features of the tensilon test:*
    (a) Duration of test is ~20 min.
    (b) Give 2 mg and watch for side effects (test dose) and then after 20s–30s give 8 mg (so total dose is 10 mg of test).
    (c) Choose clinical symptoms that can be quantify (e.g., degree of ptosis).
    (d) During test, always monitor patient's vitals for bradycardia and hypotension.
    (e) Perform test with atropine at bedside.
- *Imaging:*
  - CXR – to rule out aspiration pneumonia
  - CT chest/MRI chest – to look for thymoma

Table 5.3 Diagnosis of the myasthenia gravis [26]

Repetitive nerve stimulation test:
Also called electrophysiological testing Repetitive low rate stimulation of peripheral nerve (6–10 times) @2–3/s cause rapid reduction (>10%) of the CMAP amplitude In MG there is decremental response (i.e., progressive decline of the CMAP amplitude with the first 4–5 stimuli) A decrement of >10% when comparing the fifth to the first response is abnormal and diagnostic of MG
Single fiber electromyography test:
Most sensitive for MG, however technically more difficult than RNS Increased "jitter" with blocking is seen in NMJ disorders Confirmatory however not specific
Tensilon test:
Produce transient improvement of the weakness with neostigmine or edrophonium More sensitive than SF-EMG or RNS
Serology:
Positive AchR antibody is *highly specific test*. Presence of AchR antibody is diagnostic of MG Negative test does not rule out MG Other antibodies are MuSK antibodies (~50%) and LRP-4 antibodies (~10%)

Table 5.4 Approximate *sensitivity* of the confirmatory tests for the MG [25]

	Generalized myasthenia	Ocular myasthenia
Ice pack test	–	82%
Tensilon test	95%	85%
AchR antibodies positive	80–90%	40–55%
MuSK antibodies positive with negative AchR antibodies	40–50%	<10%
RNS	75%	<50%
SF-EMG	92–99%	80–95%

AchR acetylcholine receptor, *MuSK* muscle-specific tyrosine kinase, *RNS* repetitive nerve stimulation, *SF-EMG* single fiber electromyography

- *Diagnostic:*
  - Serology: AchR receptor antibody, anti-MuSK antibody, and anti-LRP-4 antibody.
  - Electrodiagnostic: RNS, and SF-EMG; summarized in Table 5.3.
  - Approximate sensitivity of the various tests is mentioned in Table 5.4.

It is important to note that normal stimulation rate of a peripheral nerve is 5–10/s which is same was a normal physiologic stimulation of the nerve. However, during myasthenia gravis, during testing we stimulate the nerve slower giving more time to recover from the previous stimulus.

Jitter: It's the variability in time between the two successive action potential produced by fibers connected to the same motor unit.

Silent Features of Different Types of Myasthenias [27]

- Clinical features of the AchR-antibody negative and MuSK antibodies positive MG:
  - Affects all age group
  - Female >male
  - Mostly present as generalized MG or oculo-bulbar MG with high propensity to affect respiratory muscles; thus, we see higher frequency of myasthenic crisis in MuSK antibody positive patients.
  - Pure ocular-type MG is rare. Thus, it is important to note that diplopia and ptosis is common, however not the only symptoms for MuSK antibody positive MG.
  - Possible increase jitter in neck extensor or shoulder muscles in contrast to MG in which abnormal jitter is almost always found in arm or face muscles.
  - Outcome of the MuSK antibody positive MG patients have similar outcome as AchR antibody positive in terms of prognosis and severity.
  - No association with thymic pathology.
- Clinical features of the LRP4 antibody positive patients.
  - Found in ~10% (2–50%) patient who are seronegative for both AchR and MuSK antibodies.
  - Younger patients.
  - Female > male.
  - Milder form of disease, however often presents with isolated ocular weakness or isolated neck extensor muscle weakness. Severe form of diseases is also reported.
  - No association with thymic pathology.
  - Respond well to pyridostigmine or prednisone.
- Clinical features of the seronegative MG (SNMG):
  - Similar presentation as of SPMG, but no antibodies were detected; however, electrophysiological testing is consistent with NMJ disorder.
  - Usually milder form of disease, with good response to treatment.
  - It is important to note that antibodies against titin and or ryanodine can also produce late onset MG. Presence of these antibodies carries poor prognosis with more severe disease.

Recommendation for ICU Admission

- Impending respiratory failure
- Myasthenia crisis
- Cholinergic crisis
- Others: PLEX planned, requiring frequent examination

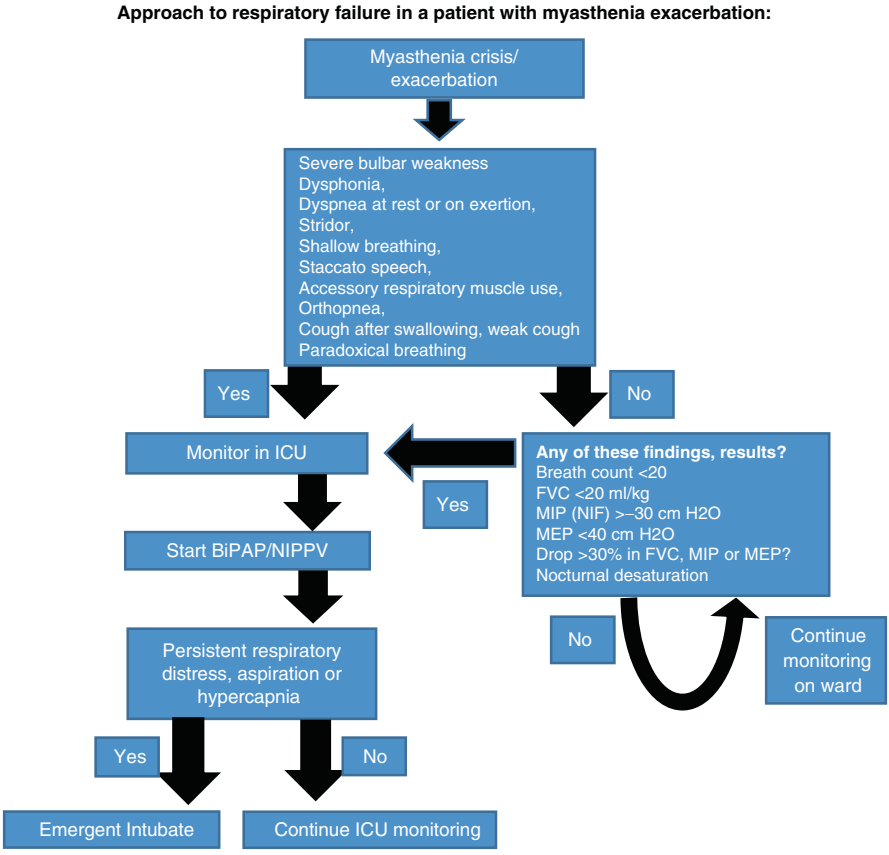

Fig. 5.2 Approach to respiratory failure in a patient with myasthenia exacerbation. (Adapted from Sleep Disorder in Neuromuscular Disorders a Clinical Guide by Raghav Govindarajan)

Predictors of Mechanical Ventilation in Myasthenia Gravis [28, 29]

Main reason for the ICU admission in the MG patients:

- *Assessment of intubation:*
  - It is important to note that some MG patients can avert intubation by using NIPPV such as BiPAP; hence, NIPPV is always considered early to avoid intubation. However, inability to maintain secretions, with myasthenic crisis, makes NIPVP a suboptimal choice, and intubation is preferred.
- *High risk for future intubation/impending respiratory failure is:* Fig. 5.2 summarizes the overall approach to respiratory failure in a patient with myasthenia exacerbation. *(Overall approach is similar to GBS.)*

- *ABG:*
  (a) PaO2 < 70 on room air.
  (b) PaCO2 > 45 or significant increase.
  (c) ABG become abnormal late in the course of NMJ respiratory failure.
  (d) If on ABG: pH and HCO2 are elevated with normal PaO2 and PaCO2; it indicates nocturnal hypoventilation, which could be as sign of early muscle weakness.
- *PFT:*
  (a) Frequent respiratory evaluation: q 2–4 h while awake; q 4–6 h when asleep.
  (b) *Rule of 20–30–40-50.* [26, 27]:
  (c) Intubate if anyone is present:
    - Forced vital capacity <20 mL/kg (Normal VC is 60–70 mL/kg).
    - Maximal inspiratory pressure (NIF) < − 30 cm of H2O (normal -80 cm H2O in male, −70 cm H20 in female).
    - Maximal expiratory pressure < 40 cm H2O (normal 100 cm H20 in adults).
    - Decrease of anyone of above >30–50% in 24 hrs.
    - For a patient with neuromuscular disorder, usually standing or leaning forward FVC and MIP >FVC and MIP in supine position. However, a drop of >20% from upright to supine positions suggests diaphragmatic weakness.
- *Single breath test:*
  (a) Count as high as possible in one breath
  (b) Able to count >25 in single breath = FVC ~ > 2 L
  (c) Able to count >10 in single breath = FVC ~ > 1 L
  (d) If there is >25% decrease in FVC when supine suggest significant diaphragmatic weakness
- *Bulbar weakness:*
  (a) Weak cough and gag
  (b) Dysphagia
  (c) Cough after swallowing
  (d) Severe dysarthria
  (e) Facial weakness
- *Other:*
  (a) Lobar atelectasis
  (b) Pneumonia
  (c) Unilateral diaphragm palsy
  (d) BiPAP is contraindicated

- Few considerations during intubation in the MG patients:
  - In myasthenia, unlike GBS, there is decreased number of the AchR, and thus succinylcholine is safe. Dose of the succinylcholine required for the intubation is ~2.5 times the dose for the same effect. Non-depolarizing agents are also safe in myasthenia but have prolonged duration affects due to increased sensitivity toward non-depolarizing agents. *Hence, when intubation is necessary in MG patients: use lower doses (~ 50% dose reduction) of non-depolarizing blocking agents.*

Independent Predictors/Risk Factors of Prolonged Intubation (>2 Weeks) in Myasthenia Gravis: [33]

- Age > 50 years
- Pre-intubation serum bicarbonate ≥30 mg/dL
- Peak VC day 1–6 post-intubation <25 mL/kg
- The proportion of patients intubated for >2 weeks was:
  - 0 risk factor: 0%
  - 1 risk factor: 21%
  - 2 risk factors: 46%
  - 3 risk factors: 88%

Weaning criteria

- Strength improving on confrontation testing
- FVC >10 mL/kg or NIF > –20 cmH2O

Extubation criteria

- Vital capacity >15 mL/kg
- Maximal inspiratory pressure > −30 cm H2O
- Satisfactory oxygenation
- Minimal pressure support
- Minimal secretions.
- Passing SBT 5/5 for >2 hr

Treatment of the MG [30]

1. Anticholinesterase therapy:
   - Pyridostigmine bromide (mestinon)
     - Usually, first line of treatment
     - Dosage: Starting dose: 30–60 mg q6h ➔ titrate slowly and accordingly to 60–120 mg q4–6 h (total daily dose not to exceed 600 mg)
     - Risk of cholinergic crisis with doses larger than 120 mg every 2 hours
   - Slow-release pyridostigmine bromide (timespan); has longer duration of action
   - 180 mg timed-release pyridostigmine can be given at night in case of severe weakness upon awakening

     Note: Anticholinesterase therapy is for symptomatic treatment and thus can be stopped in intubated patient. Also, MuSK positive patient usually did not respond or have intolerance to anticholinesterase therapy.
2. Prednisone:
   - Recommended in all cases of moderate to severe MG and inadequately responding MG to cholinesterase inhibitors
   - Onset of action is usually days to weeks and peak action is around 4–8 weeks
   - Regime/dosage:
   - For moderate to severe generalized MG

  - High-dose regime (1 mg/kg or 60–100 mg daily; often combined with IVIG or plasma exchange)
- Adverse effect: ~30–50% of patients transiently become worse (occurs in patients taking high dose regime or taking prednisone for first time), hence be watchful for possible intubation; psychosis, pseudotumor cerebri, sleep disturbances, hypertension, glaucoma, and hyperglycemia (be watchful in diabetic patients)
- *Preventive measures for complications of high-dose prednisone should be considered*
  - Hypokalemia (routine labs including CBC and CMP)
  - Avoidance of extra dietary salt
  - Routine Peptic ulcer ppx
  - Calcium and vitamin D supplement to counteract osteoporosis
  - Prophylactic anti-tuberculosis antibiotics for tuberculin-positive patients (CXR)
  - If indicated: *Pneumocystis jiroveci* pneumonia prophylaxis with trimethoprim-sulfamethoxazole (bactrim)
  - Routine screening as outpatient for osteoporosis (Dexa scans), cataracts, glaucoma (eye examination), hypertension, diabetes mellitus

3. Azathioprine
   - Indication:
     - First line for: Patient's at high risk for corticosteroid-induced side effects (postmenopausal, DM, elderly, glaucoma) and suffering from moderate to severe MG (in combination of the steroid).
     - Patient with inadequate response to the above treatment.
   - Onset: slow (over 4–12 months;?? disadvantage).
   - Dosage: Starting dose: 2–3 mg/kg; maintain dose: 2 mg/kg daily.
   - Adverse effects: mild leukopenia and macrocytosis (dose dependent), reversible liver enzyme elevation, dose-dependent reversible bone marrow suppression, pancreatitis, increased risk of malignancy and infection. *Note: Dosage should be reduced if WBC ≤ 4000; and stop if WBC ≤ 3000.*
4. Other steroid sparing drugs were:
   - Cyclophosphamide (Cytoxan), Mycophenolate mofetil (CellCept), tacrolimus, cyclosporine and rituximab.
   - *Rituximab can be used as monotherapy in MG. It is recommended that rituximab should be considered in refractory patients as steroid-sparing therapy and in patients with MuSK antibodies.*
5. Plasma exchange (PLEX)
   - 1 volume q 1–2 days for five exchanges.
   - Plasma exchange removed circulating antibodies, complement and soluble biological response modifier.
   - With plasma exchange, there is early improvement in muscle strength and reduce need for mechanical ventilation and better recovery.

- *Side effects and contraindications:* Hypocalcemia, transfusion reaction, hypotension, infection, pneumothorax, and hematoma. C/I in septic shock, MI within 6 months, active bleeding, and *marked dysautonomia.*
- PLEX is also used for myasthenic crisis and to optimize muscle function before a surgical procedure, including thymectomy.

6. Intravenous immunoglobulin (IVIg) [31]
   - IVIG dose: 0.4 mg/kg q 1 day × 5 days (effective up to 2 months).
   - IVIG is as effective as plasma exchange for moderate to severe MG.
   - IVIG precise mechanism is unknown; however, it is postulated that it may provide anti-idiotypic antibodies, modulating expression, and function of Fc receptors, interfering with activation of complement, interfering with production of cytokines, and interfering with activation and effective function of T and B cells.
   - Patients with more severe clinical disease may benefit for longer duration of IVIG treatment.
   - IVIG is associated with lower complication rate.
   - *Side effects and contraindications:*
     – Anaphylaxis in IgA-deficient patient (always check IgA level)
     – General: Flu like symptoms; nervous system: aseptic meningitis, HA, reversible encephalopathy; cardiovascular: hypertension, chest pain, and thromboembolism Contraindicated in CHF, and renal insufficiency. Renal: AKI. GI nausea and vomiting
7. Thymectomy [32]
   - Recommended to the patients with thymoma (clear benefit was reported)
   - Can be done in patient without thymoma however the data remain controversial
   - Recommended for most patients younger than 60 years
   - Not recommended for patients older than 60 years due to usually higher surgical morbidity
   - Not recommended for MuSK antibody positive patients

Critical Care Illness Neuropathy & Myopathy

Definition

Critical care illness neuropathies and myopathies are one of the common complications witnessed in the intensive care unit (ICU) setting. Though it affects a higher percentage of patients admitted to the ICU, it still lacks a universal definition. Stevens et al. defined it as the occurrence of new clinical weakness in ICU admitted patients, with no other identifiable causes other than the critical illness itself [34]. They constitute a group of disorders that are indistinguishable by physical examination, requiring electrophysiological investigations for diagnosis and differentiation. These include critical illness neuropathy (CIP), critical illness myopathy (CIM), and critical illness neuromyopathies [35].

Epidemiology

Critical care illness neuropathies and myopathies affect the peripheral motor axons more than the sensory and attack the muscles as well. A systematic review by Appleton et al. determined that weakness in ICU-admitted patients has an approximate incidence of 40%. The study took into consideration characteristics like study population, risk factors, diagnostic technique, and incomplete evaluation resulting in underreporting [36]. A prospective cohort study by Hermans et al. involving 415 post-surgical patients with ICU stay of more than 7 days showed that the incidence of patients affected with weakness was 55% [37]. The true incidence of the condition is still not known and can range from 50% to 100% of the patients, affecting each patient to varying degrees [38].

Pathophysiology

Critical care illness neuropathies and myopathies are diseases that have a multifactorial etiology and are more severe when the patient has multiple organ dysfunction or failure. CIP or CIM occurs as separate entity or overlap with each other, the cause of which is unclear. The precise pathophysiological mechanism of the condition is still not well understood and multiple theories have been postulated. A few of these include the following:

- Altered microcirculation- Increased E-selectin expression in vascular endothelium of peripheral nerves causes leukocyte activation and increase in vascular permeability. This results in endoneural edema and increased cytokine production resulting in nerve damage. The hypoxic ischemia that occurs can also result in damage of the muscle fibers.
- Altered metabolic supply – metabolic diseases alter nutrient and vascular supply to nerves resulting in axonal degeneration from hypoxic ischemia [39].
- Altered cellular function – increase in pro-inflammatory cytokines results in increased production of reactive oxygen species and a reduction in antioxidants. This affects the functioning of the mitochondria and hence causing axonal ATP depletion [40].
- Acquired channelopathy – repetitive firing of motor neurons is seen in the early stages of inflammation. This is followed by function failure and development of acquired channelopathy of voltage-gated sodium channels which ultimately results in nerve non-excitability, altering the calcium homeostasis causing calcium overload, followed by axonal degeneration [41].

Risk Factors

Multiple risk factors that increase the occurrence of ICU acquired weakness have been identified in literature. These have been reviewed below:

- Sepsis: Severity of the illness seems to play a crucial role in the development of ICU associated weakness. Hence there is an increased occurrence of CIP/CIM in patients with septic shock and multiple organ failure [42]. Studies show that ATP depletion and bioenergetic failure may be the predominant pathophysiological mechanism in affected patients [43].
- Immobilization: Immobility in critically ill patients results in disuse atrophy of muscles, and these patients have normal electrophysiological studies [44].
- Drugs: Neuromuscular blocking agents are used to aid mechanical ventilation, and metabolism of these drugs is impaired in the setting of organ failure, which results in prolonged drug effects and resultant weakness [45]. Some studies show aminoglycosides can result in peripheral nerve dysfunction; however, this lacks enough statistical proof [46]. Corticosteroids, vasopressors, and catecholamines have also been identified as independent risk factors in prospective studies [47].
- Metabolic derangements: Hyperglycemia causes elevated glucose levels in cells and increased oxidative stress, damaging nerve tissue. This further also causes myofibrillar degeneration and muscle atrophy through activation of degradation pathways [48]. Hypoalbuminemia causes worsening of the changes in microcirculation resulting in ischemic damage to both the nerve and muscles [49].
- Other risk factors: Old age, hyperosmolality, and renal replacement therapy are others that can increase incidence of CIP/CIM [35].

Clinical Presentation

The development of generalized weakness in ICU-admitted patients can range from mild to a more severe form called ICU-acquired paresis [50]. Symmetric flaccid quadriplegia, muscle atrophy, and reduced or absent deep tendon reflexes are also detected on examination [51]. Sensory impairment seen in patients is less severe in comparison to the motor weakness that is observed [35].

Diagnosis

CIM/CIP is a condition that can be diagnosed by a thorough neurological examination and neurodiagnostic tests.

Clinical Assessment

When evaluating patients with CIP/CIM, it is important to know if the patient developed his symptoms during his stay at the ICU or he has been having it even before his admission. The presence of weakness prior to admission may indicate the need to analyze other causes of weakness like Guillain-Barre syndrome, myasthenia gravis, and amyotrophic lateral sclerosis, to name a few.

A standard Medical Research Council (MRC) scale is used by clinicians for bedside assessment of motor strength in six major muscle groups bilaterally (Table 5.5). *The maximum score is 60 points and a score of less than 48 is*

Table 5.5 MRC scale for strength assessment [51]

Muscle groups assessed	*Scoring*
Shoulder abduction	Movement against gravity and full resistance [5]
Elbow flexion	Movement against gravity and some resistance [4]
Wrist extension	Movement against gravity but not resistance [3]
Hip flexion	Movement not against gravity [2]
Knee extension	Contraction without movement [1]
Ankle dorsiflexion	No contraction (0)

Table 5.6 Electrophysiological findings in CIP/CIM [52]

Subtype	*CMAP*	*SNAP*	*MUP*	*CMAP ratio*
CIP	Low amplitude	Low amplitude	Reduced recruitment	<0.5
CIM	Low amplitude	Normal	Early full recruitment, short duration, low amplitude	>0.5

considered diagnostic [52]. In patients who are unable to participate in the examination of the major muscle groups, handgrip strength may be used as a substitute to gauge weakness [53]. Sensory impairment can be elicited in affected individuals; however, it is less severe in comparison to motor damage. Involvement of respiratory muscles prolongs weaning from mechanical ventilation and limb paralysis requires physical rehabilitation for longer time-periods [42].

Electrodiagnostic Studies

Nerve conduction studies and electromyography (EMG) help in diagnostic confirmation of CIP/CIM as well as distinguish it from other neuromuscular causes. Measuring the compound muscle action potential (CMAP), the sensory nerve action potential (SNAP), and the motor unit potentials (MUP) aid in the diagnosis of the condition (Table 5.6). CMAP ratio and MUP are reliable parameters to differentiate between a nerve and muscular etiology.

Muscle Biopsy

- CIP: Acute denervation with atrophy of muscle fibers
- CIM: Varying necrosis with selective loss of thick myosin filaments
- Critical illness neuromyopathies: Generalized necrosis [44]

Treatment

Effective therapeutic options for CIP/CIM is scarce, and avoidance of risk factors are essential to reduce the occurrence of ICU acquired weakness. It contributes to increased disability, eventually leading to poor quality of life.

- Early mobilization: Studies have shown that early rehabilitation can help improve the functional outcome in critically ill patients. Though this seems promising several barriers identified at patient, provider and organizational levels may hinder the implementation of early mobilization [53].
- Glycemic control: Several studies have shown that intensive insulin therapy in ICU patients have shown to reduce the incidence of CIP/CIM, decrease the number of days requiring mechanical ventilation, as well as improving long-term benefits.
- Management of sepsis: Efforts to avoid sepsis and its complications as well as aggressive treatment if it occurs is indicated in these patients.
- Drugs and nutrition: Critically ill patients have poor nutrition and so maintaining a good nutritional supply helps prevent muscle atrophy and eventually weakness. Drugs like steroids, neuromuscular blockers, and sedatives should be used by weighing the benefits against possible side effects [54].

Amyothopic Lateral Sclerosis (ALS) & Respiratory Failure

- Amyothopic lateral sclerosis (ALS) is the most common motor neuron disease in adults, with an estimated prevalence of 5.2 cases per 100,000 people [55].
- Ninety-five percent of cases are sporadic, due to unknown etiology. Familial cases are predominantly autosomal dominant, but other inheritance patterns have been implicated.
- Hallmark features of ALS include simultaneous upper motor neuron (UMN) and lower motor neuron (LMN) defects in 1 or more body regions. Diagnosis is primarily clinical, but EMG testing is often performed.
- Despite the progressive course and poor prognosis, chronic therapy with riluzole (a glutamate antagonist) and adequate management of complications have been associated with prolonged survival. A recently FDA-approved drug edaravone has been associated with better short-term functional outcome.
- Symptomatic management should be multidisciplinary and proactive, looking for any new dysfunction that may require change in therapeutic approach. The most commonly reported symptoms are sialorrhea, pseudobulbar affect, muscle cramps, spasticity, and dyspnea.
- *Sialorrhea* often develops as a consequence of impaired swallowing and facial muscle weakness. Initial therapies include oral atropine drops, oral amitriptyline, oral or transdermal hyoscine (scopolamine). Refractory cases may benefit from botulinum toxin injections to salivary glands and, lastly, from irradiation of salivary glands [56].
- *Pseudobulbar affect*, or emotional liability, occurs in about half of ALS patients, irrespective of bulbar motor symptoms. Effective therapies comprise dextromethorphan-quinidine, amitriptyline, and SSRIs such as fluvoxamine [56].
- *Muscle cramps* may benefit from multiprofessional approach, including physical therapy and/or hydrotherapy. Although latest guidelines have limited medical therapy to antiepileptics such as levetiracetam and carbamazepam, recent trial

evidence supports the use of the antiarrhtythmic mexiletine for muscle cramps in ALS (62;67).

- *Spasticity* in ALS also benefits from combined medical and physical therapies. Initial treatment with antispasmodics such as baclofen or tizanidine is recommended. In refractory cases, intrathecal baclofen may provide additional effect [56].
- *Dyspnea* and *dysphagia* are the most concerning issues in ALS patients and also require a multidisciplinary approach. They will be discussed separately in the respiratory management and nutrition management sections, respectively.

Respiratory Management

- Respiratory monitoring starts soon after ALS diagnosis, by assessing baseline respiratory status through clinical exam and pulmonary function tests (PFTs). Nocturnal oximetry, forced vital capacity (FVC), and maximal inspiratory pressure (MIP) are widely used to detect hypoventilation and to guide decisions to supplement chronic respiratory management in these patients, summarized in Fig. 5.3 [57].
- Supportive measures like psychosocial support, modification in activity level, chest physiotherapy are important at any stage of the disease.
- *Secretion management* is a fundamental to respiratory management since expiratory respiratory muscle weakness may lead to ineffective cough, retained secretions, aspiration, and pneumonia.
- The only evidence-based effective approach for secretions in ALS is mechanical insufflation/exsufflation (MIE), but other therapies have also been typically used:

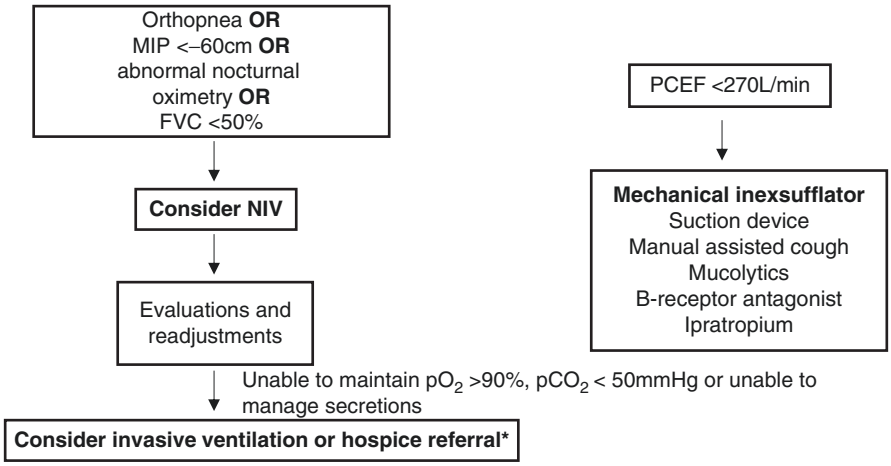

Fig. 5.3 Chronic respiratory management in ALS. MIP maximal inspiratory pressure, FVC forced vital capacity, NIV noninvasive ventilation, PCEF peak cough expiratory flow. *Hospice referral may be sought out earlier if patient doesn't tolerate or accept NIV

mucolytics, B-receptor antagonists such as propranolol or metoprolol, nebulized short-action anticholinergics like ipratropium [57].
- Dyspnea is often associated with anxiety, especially as the disease progresses, and palliative measures are fundamental even at earlier ALS stages. Intermittent bouts of dyspnea may be alleviated with sublingual lorazepam. Chronic dyspnea can benefit from oral, subcutaneous, or intravenous morphine [56].
- Although ALS respiratory compromise tends to appear late, some patients will have early respiratory failure as the first manifestation. These patients often need intensive care management with early invasive ventilation (IV), but respiratory function may improve to ventilator independence after a short course of ventilatory support with adequate rest [58].
- Regardless of the disease stage, acute respiratory failure in ALS should always be thoroughly investigated for reversible causes, due to the aforementioned risk factors for pulmonary complications.

Nutrition Management

- Dysphagia is one of the major concerning issues in ALS patients. It may worsen muscle weakness due to reduced caloric intake and may increase the risk of aspiration and respiratory complications.
- Dysphagia and nutritional status should be evaluated at every visit in the earlier stages of ALS. As soon as the first signs of dysphagia appear, early referral to a speech therapist and a dietitian will provide adjustments on swallowing technique and modifications of food and fluid consistencies, respectively. Ultimately, patients may benefit from percutaneous endoscopic gastrostomy (PEG).
- PEG has been proven effective in stabilizing the weight and prolonging survival. The indication for PEG placement is multifactorial, based on bulbar symptoms, weight loss, respiratory compromise, and patient's general condition. Patients with worsening dysphagia associated with more than 10% weight loss are good candidates if they have a baseline FVC more than 50% [56, 57].

Miscellaneous

1. *Spinal cord ischemia*
   - Spinal cord ischemia (SCI) is a rare but potentially disabling condition with a wide spectrum of etiologies. Incidence has been estimated as 3.1 per 100,000 person-years [59].
   - Most cases are secondary to thoracoabdominal aorta primary or secondary injury, but systemic hypotension and vascular malformations are also prominent causes.

Clinical manifestations are strongly related to the vascular territories involved, which can be divided in anterior and posterior. Anterior vascular supply is provided

Table 5.7 Spinal ischemic syndromes

Anterior spinal artery ischemia	Bilateral motor deficit/spinothalamic sensory deficit
Anterior unilateral ischemia	Hemiparesis/contralateral spinothalamic sensory deficit
Posterior unilateral ischemia	Ipsilateral lemniscal sensory deficit +/− hemiparesis
Central cord ischemia	Bilateral spinothalamic sensory deficit
Posterior spinal artery ischemia	Lemniscal sensory deficit +/− bilateral motor deficit
Transverse ischemia	Bilateral motor and sensory deficit

by an arterial spinal artery (ASA) and its sulcar arteries, while posterior vascular supply is derived from two posterior spinal arteries (PSAs). The main spinal ischemic syndromes are represented in Table 5.7.

- Lesions affecting ASA will produce a biphasic deficit below the injury level, resembling spinal shock: initial lower motor neuron (LMN) symptoms followed by superior motor neuron (SMN) symptoms.
- Cervical and upper thoracic cord involvement is particularly concerning in anterior syndromes due to potential quadriparesis and diaphragmatic weakness, leading to acute respiratory failure. These lesions may also produce cardiovascular abnormalities, like neurogenic shock, secondary to autonomic fiber involvement. Due to the aforementioned reasons, patients with cervical or thoracic SCI should be considered for ICU management with close monitoring of vitals and neurologic status.
- Diagnosis is traditionally based on history of acute onset myelopathy in the absence of another more likely etiology through clinical or radiologic assessment. Recently proposed criteria also included non-inflammatory CSF as a supporting evidence of SCI [60].
- Clinical management of SCI is mostly limited to assuring adequate blood pressure and ventilation. Cervical and thoracic SCI require proactive respiratory management including chest physiotherapy, frequent suctioning, and invasive ventilation upon the first signs of impending respiratory failure.
- Prophylactic measures targeting risks of immobilization also play an important role in management of patients SCI. Due to the higher risk of venous thromboembolism (VTE) and pressure sores, most patients benefit from chemical VTE prophylaxis, frequent patient repositioning, besides physical and occupational therapies. The high incidence of urinary disturbances in the acute phase of SCI may require early urinary catheterization.

2. *Traumatic spinal cord injury*
   - Trauma is the most common cause of acute spinal cord injury and is estimated to affect 40 per every 1,000,000 people in the United States [61].
   - There are two phases of injury to the CNS in the setting of trauma. A primary injury is directly related to the mechanical forces caused by the trauma. A secondary phase starts shortly after the primary injury and is associated with several factors such as vascular injury, ionic imbalance, excitotoxicity, and inflammation.
   - All therapeutic efforts should try to minimize primary injury and prevent secondary injury as much as possible. Besides providing standard trauma care,

management should involve acute management of complications, and imaging assessment for signs of primary injury that may require surgical intervention.
- Intensive care is often necessary in spinal cord trauma (SCT). Patients with SCT are at increased risk for organ dysfunction, likely secondary to systemic inflammation. Furthermore, cervical and upper thoracic spine injuries may cause cardiovascular and respiratory complications [61].
- Blood pressure requires more aggressive care in SCT than in other types of spinal cord injury, especially during surgical interventions. Mean arterial pressure (MAP) should be aimed for 85 mmHg, except in cases of concurrent traumatic brain injury (TBI) with intracranial pressure (ICP) abnormalities.
- Although previously recommended, use of steroid infusion in the acute phase of SCT has become debatable. There is weak evidence supporting methylprednisolone infusion if initiated within first 8 h after SCT [62].

3. *Spinal cord tumor*
   - Spinal cord tumors are relatively rare among CNS tumors but may cause irreversible disability if untreated. Most cases (69–78%) are nonmalignant, and incidence rates for malignant and nonmalignant spinal tumors are 0.22 per 100,000 persons and 0.76 per 100,000 persons, respectively [63, 64].
   - These tumors are classified as extradural or intradural, and the latter may be further divided into extramedullary or intramedullary according to the involvement of spinal cord parenchyma.
   - Clinical features suggestive of spinal cord neoplasia include focal or radiating pain that may cause nocturnal awakening, as well as unilateral or bilateral neurologic deficits distal to the lesion. Symptoms usually emerge in a chronic progressive fashion, but acute presentations are possible, for instance, in pathologic fractures.
   - Diagnosis should be complemented by neuroimaging, ideally contrast-enhanced MRI
   - Management of spinal cord tumors will differ according to the histologic type and axial localization. Intramedullary tumors usually require total or subtotal resection, sometimes followed by radiation therapy. Extramedullary tumors have a higher threshold for surgical intervention, more often required in large-sized or symptomatic tumors.
   - Extradural tumors should be intensively managed due to the potential of reversible spinal cord compression injury in earlier stages. Management may include steroid infusion with prolonged taper, surgical intervention, and radiation therapy.
   - As in other types of spinal injury, intensive care may be needed in acute presentations involving cervical and upper thoracic spinal levels.
4. *Epidural abscess*
   - Spinal epidural abscess (SEA) is among the rarest forms of back pain, with incidence ranging from 2.5 to 3 per 10,000 hospital admissions [65].
   - Commonly attributed risk factors include diabetes, intravenous drug use, alcohol abuse, recent trauma or surgery, and local or systemic infections [66].

- SEA usually develops secondary to hematogenous spread from distant foci, and less likely from contiguous spread or direct inoculation.
- Patients usually present with acute or subacute back pain, with fever being reported in about half of the cases. Weakness, radiculopathy, bowel/bladder dysfunction, and other neurological findings are reported in less than half of patients. Since some of these neurological findings are not rarely seen in critically ill patients, ruling out SEA is of great importance.
- Neuroimaging is an essential component for diagnosis and delimitation of SEA. Gadolinium-enhanced MRI is preferred, but contrast CT may be alternatively used. If findings are compatible with SEA, two sets of blood should be sent for cultures.
- CT-guided abscess drainage should be sought except when commonly implicated organisms such as *S. aureus* have been recently isolated. Lumbar punctures should be avoided due to the low diagnostic yield and the potential for subarachnoid spread of infection.
- Management of SEA starts by early initiation of empiric antibiotics, ideally after blood cultures are sent. *Staphylococci*, *Streptococci*, and gram-negative coverage are recommended. Duration of empiric and sensitivity-guided antibiotics may range from 4 to 16 weeks, depending on the presence of comorbidities such as vertebral osteomyelitis.
- Most cases will also benefit from early surgical decompression (within 24 h after diagnosis), due to the risk of sepsis and neurologic sequelae.
- Although the prognosis of SEA has historically improved due to the advents of antibiotics and new imaging technologies, many patients still have a late diagnosis. The outcome is still strongly related to the time of diagnosis and surgical intervention.

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Anesthesia-Related Complications in Neuromuscular Disorders in Adults

6

Hariharan Regunath, Kyle Ludwig, and Stevan P. Whitt

Introduction

Anesthesia for neuromuscular disorders (NMD) is associated with high risk for several complications in the peri-operative period including the worsening of respiratory failure and exacerbation of heart failure [1]. Depolarizing paralytics and volatile sedatives are associated with high risk for life-threatening complications such as malignant hyperthermia (MH), severe hyperkalemia, and rhabdomyolysis [1–3]. Outcome depends on proper pre-operative assessment and optimization of medications and medical disorders, type of anesthesia (general or regional anesthesia), choice of sedatives and paralytic agents, cardio-respiratory functional reserve, and

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risk of aspiration [1]. A multidisciplinary approach is recommended to optimize outcomes [2]. In this chapter, we discuss pre-operative risk assessment, an overview of complications of anesthestic administration in patients with NMD and peri-operative considerations of optimal care.

Overview of Neuromuscular Diseases

Hereditary and acquired NMD can be classified based upon the rapidity of onset (acute or chronic), level of neuraxial involvement (Spinal cord/neuropathic [presynaptic], neuromuscular junction [synaptic] or muscular/myopathic [post synaptic]), and rate of progression [4]. Table 6.1 lists the various NMD that can

Table 6.1 Neuromuscular diseases causing cardio-respiratory dysfunction

Onset	Spinal cord/ neuropathic disorders	Neuromuscular junction disorders	Myopathic disorders
Acute	Guillian-Barre syndrome[a] Cervical spinal cord injury[a] Critical illness neuropathy Multiple sclerosis Transverse myelitis[a] Epidural abscess Acute poliomyelitis Paralytic rabies	Myasthenia gravis[a] Lambert-Eaton myasthenic syndrome Congenital myasthenic syndrome Botulism Venoms (snake, scorpions, ticks) Neuromuscular junction blockers Organophosphorus poisoning	Corticosteroids Critical illness myopathy
Chronic	Spinal cord injury[a] Motor neuron diseases Amyotrophic lateral sclerosis[a] Spinal muscular atrophy Post-polio syndrome Chronic inflammatory demyelinating polyneuropathy Charcot Marie tooth disease		Muscular dystrophies[a] Duchenne muscular dystrophy Becker muscular dystrophy Fascioscapulohumeral muscular dystrophy Oculopharyngeal muscular dystrophy Myotonic dystrophy Other congenital dystrophies (Ulrich, Bethlem, Merosin-deficiency, Emery-Dreifus, Fukuyama, central core, nemaline, etc.) Inflammatory myopathies[a] Polymyositis Dermatomyositis Toxic Metabolic myopathies[a] Glycogen storage disorders Mitochondrial myopathies Lipid storage Endocrine myopathies

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[a]NMD with cardiac dysfunction including dysautonomia, arrhythmias, cardiomyopathies, conduction abnormalities and long QT syndromes

cause respiratory dysfunction, primarily from progressive failure of respiratory mechanics leading into a vicious cycle of hypo-ventilation causing atelectasis that further increases the load of respiration [4, 5]. Varying degrees of cardiac involvement occurs in inherited NMD in the form of a cardiomyopathy and/or conduction disorders, the onset and severity of which is affected by characteristics specific to the sequelae of the genetic abnormalities affecting the cardiac muscle cytoskeleton and its function [5, 6]. Cognitive dysfunction can also be seen in certain neuromuscular diseases [7]. Hence accurate diagnosis including genetic testing is imperative in inherited NMD when planning anesthesia [6]. Sometimes, genetic and other testing may not pinpoint a specific NMD, but those with a suspected diagnosis should still be considered to be at significant risk for anesthesia related complications [2, 6].

Pre-operative Evaluation and Considerations

Screening for motor function is a routine part of pre-operative assessment in all patients [8]. Those with a developmental delay, inability to walk prior to 18 months of age, with or without a family history, and kyphosis or scoliosis should be considered for referral and formal neurological evaluation [1]. Subclinical neuromuscular disorders should be considered in patients with sleep disordered breathing, recurrent pneumonia, ineffective cough, and swallowing difficulty. In those patients with an established diagnosis of NMD, surgery should be avoided in the absence of compelling indications because of the increased risk of complications in NMD [3]. There is a non-linear relationship between the rate of progression of NMD and decline/compromise of cardio-respiratory function. Sometimes cardiac manifestations may precede the onset of neuromuscular symptoms [8, 9]. Hence, pre-operative testing should be thorough and guided by the severity of neuromuscular, cardio-respiratory, and cognitive dysfunction, as well as selection of anesthesia and surgical approach [2, 3].

Pre-operative exam should focus on ominous signs of impending respiratory failure such as inability to complete sentences, paradoxical movement of abdomen, bulbar weakness, and ophthalmoplegia (e.g., myasthenia gravis) [4, 8]. In patients with an isolated twofold elevation of serum of CK, in the absence of other causes such as trauma, hypothyroidism, and/or endocrinopathies, drugs [statins, neuroleptics, etc.] or myositis should be considered at high risk for serious complications including rhabdomyolysis [1, 10]. An electrocardiogram, echocardiogram, chest X-ray, blood gas analysis, and pulmonary function tests may be necessary to accurately assess the presence and extent of impairment [3, 8]. Baseline blood counts, serum electrolytes, renal function tests, and creatine kinase (CK) levels are necessary. This information should be obtained even for those with suspected NMD. These studies, along with information regarding onset of symptoms and phenotypic characteristics, can guide risk assessment [1].

Specific Respiratory Function Tests

A baseline/daytime pulse oximeter oxygen saturation (SpO_2) <95% in room air necessitates measurement of serum carbon dioxide levels (PCO_2). A higher than normal serum bicarbonate level could serve as a surrogate of diurnal hypercapnia [4]. A peak cough flow of <270 ml/min, a forced vital capacity of <50% of predicted, daytime/diurnal hypercapnia (PCO_2 >45 mmHg), and those with concomitant nocturnal hypoventilation or sleep apnea may benefit from the use of noninvasive ventilation (NIV) and cough assist devices and techniques and pre-operative education on their use [10].

Specific Cardiac Tests

Cardiac manifestations such as heart failure may not be symptomatically evident because of physical mobility limitations posed by NMD [11, 12]. Echocardiogram can reveal regional wall motion abnormalities associated with focal fibrosis seen in hereditary myopathies or pulmonary hypertension associated with respiratory involvement in NMD. A normal echocardiogram at baseline, however, does not completely exclude the possibility of heart failure in hereditary myopathies, because some degree of cardiac muscle involvement is always present and may only become evident under the hemodynamic stress associated with surgery [13]. If surgery will be associated with such a significant hemodynamic stress, pre-operative testing with a pulmonary artery catheterization to assess fluid and inotropic responsiveness may be considered [3]. Similarly, a Holter monitor may be necessary in myopathies at risk for dysrhythmias and/or conduction defects [10].

Non-anesthetic Considerations

Pre-operative plasmapheresis may be necessary for autoimmune neuromuscular junction disorders including myasthenia gravis. However, plasma cholinesterase is responsible for the metabolism of medications such as succinylcholine, mivacurium, remifentanil, and esmolol. Following plasmapheresis, delayed clearance of these medications can lead to a prolonged recovery [2, 14]. Table 6.2 provides a common list of medications that amplify neuromuscular blockade or muscular weakness that should be avoided if possible in the pre-operative period.

Table 6.2 Non-anesthetic medications which can amplify neuromuscular blockade

Drugs	Comments
Aminoglycosides	Aminoglycosides block the presynaptic release of acetylcholine in a dose-dependent fashion. Each individual agent has its own risk. Tobramycin seems to have the least toxic effect as compared to neomycin which is the most potent [15–17]
Vancomycin	The mechanism for vancomycin potentiate neuromuscular blockade is unclear, but does seem to be an additive effect when added to other agents [18]
Quinidine (and other quinine derivatives), procainamide and disopyramide	Class I A anti-arrhythmics act by inhibiting sodium channels and increasing action potential duration. They presynaptically impair the formation or release of acetylcholine leading to muscle weakness [19, 20]
Beta-blockers	Beta adrenergic blocking agents are labeled for inducing subjective fatigue. Propranolol seems to have the greatest impairment. Atenolol seems to have the least potential [21–23]
Calcium channel blockers	Presynaptic reduction in acetylcholine release and also postsynaptic curare-like effects have been observed in experimental settings [24–27]
Corticosteroids	There seems to be a correlation between the occurrence of acute corticosteroid myopathy and the type or dose of corticosteroids administered. The fluorinated corticosteroids (triamcinolone, betamethasone) appear to be more often associated with myopathies than the non-fluorinated corticosteroids (hydrocortisone, prednisone) [28]. In regards to dosing, there is widespread variability in reports who develop weakness, but it is usually not seen at doses of 20 mg or less of prednisone equivalence [29]

Complications Associated with Anesthesia in NMD

The complications associated with anesthesia in NMD can be classified as a follows.

Muscular/Metabolic Complications

Malignant hyperthermia, rhabdomyolysis, and hyperkalemia are the most life-threatening complications.

Malignant Hyperthermia (MH)

In this disorder, the fundamental defect is in the regulation of calcium concentration within the skeletal muscles (myopathic disorders). Use of halogenated inhalational

anesthetics (halothane, sevoflurane, enflurane, isoflurane, desflurane, methoxyflurane) and/or succinylcholine in patients with skeletal muscle ryanodine RYR1 or rarely dihydropyridine (DHP) receptor abnormalities poses the highest risk for this pharmacogenetic disorder [30, 31].

Epidemiology

The overall prevalence of MH is difficult to estimate because of regional population differences, incomplete penetrance, and variable expressivity of the inherited neuromuscular disorders [32]. Data from an administrative national database of the United States reported an increasing incidence of 10.2–13.3 patients per million discharges for 2000–2005 [33]. Among New York State Hospitals (NYSH), prevalence of MH among hospital surgical patients during anesthesia was 1 in 100,000 with a male (2.5–4.5 times higher) predominance for 2001–2005 [34]. For ambulatory surgical patients in NYSH, the incidence was much less at 0.18 per 100,000 discharges 2002–2011 [35]. Overall mortality from MH is estimated to be 0.0082 per 100, 000 surgical patients in the United States (US). The North American Malignant Hyperthermia Registry of the MH association of the United States (MHAUS) reported a 2.7% cardiac arrest and 1.4% death rate among 291 MH cases reported between 1987 and 2006. This has increased to 8.3% cardiac arrests and 9.6% deaths among 189 MH cases for 2007–2012 [36]. In this recent report, most deaths were in low to intermediate risk patients with undiagnosed mutations in ryanodine receptors [36].

Pathophysiology

Exact pathophysiology is unclear, but the inciting agent perturbs the skeletal muscle calcium homeostasis leading to a viciously propagating cycle of intracellular release of calcium from the sarcoplasmic reticulum that results in hyper-metabolic generation of heat within skeletal muscle leading to life-threatening hyperthermia, rhabdomyolysis, hypercapnia, acidosis, and hyperkalemia (Fig. 6.1) [30, 37, 38].

NMD Associated with Risk for MH

The susceptibility to MH varies between the genetic variants of skeletal muscle receptors (e.g., ryanodine or dihydropyridine receptors on the sarcoplasmic reticulum) [30, 39, 40]. All ryanodinopathies (central core myopathy, multicore myopathy, Native American myopathy, King Denborough disease, and periodic hypokalemic paralysis) are considered to be at highest risk for MH (up to 30%) [41]. Because of overlap of NMD phenotype-genotype combinations, all patients with suspected ryanodine receptor abnormalities should be considered high risk unless proven otherwise by testing (caffeine halothane contracture test [CHCT]) [41, 42]. Those with a suspected subclinical myopathy, exercise- or stress induced fever and/or rhabdomyolysis, and family or personal history of adverse reactions to anesthesia such as acidosis, jaw stiffness, myoglobinuria, hyperthermia, etc. can be healthy carriers of RYR1 or DHP receptors and hence still considered to be at risk for MH [1, 10, 43, 44]. Appropriate diagnostic investigations and precautions must be undertaken; a diagnostic algorithm is available from the MHAUS for evaluating patients at risk for MH [37].

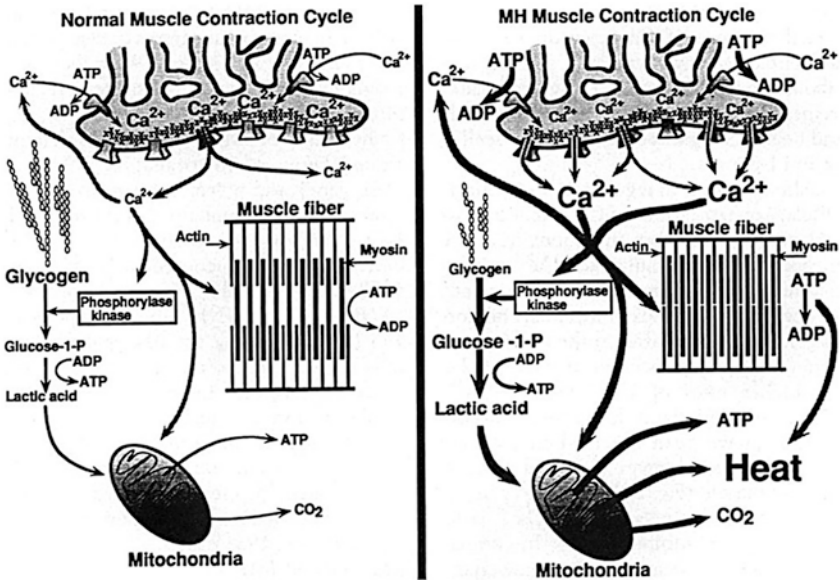

Fig. 6.1 Proposed mechanism for induction of malignant hyperthermia. In a normal relaxation-contraction cycle (left), Ca^{2+} is pumped into the sarcoplasmic reticulum by a Ca^{2+} ATPase to initiate relaxation, stored within the lumen in association with calsequestrin, and released through a Ca^{2+} release channel to initiate contraction. Glycolytic and aerobic metabolisms proceed only rapidly enough to maintain the energy balance of the cell. The Ca^{2+} release channel can be regulated by Ca^{2+} itself, ATP, Mg24, and calmodulin and, even when stimulated, has a relatively short open time. The abnormal malignant hyperthermia Ca^{2+} release channel (right) is sensitive to lower concentrations of stimulators of opening, releases Ca^{2+} at enhanced rates, and does not close readily. The abnormal channel floods the cell with Ca^{2+} and overpowers the Ca^{2+} pump that ordinarily lowers cytoplasmic Ca^{2+}. Sustained muscle contraction accounts for rigidity, and sustained glycolytic and aerobic metabolism account for the generation of lactic acid, CO_2, and heat and enhanced oxygen uptake. Damage to cell membranes and imbalances of ion transport can account for the life-threatening systemic problems that appear during a malignant hyperthermia episode. (Reprinted with permission from Mclennan et al. Science 1992; 256:789. Copyright 1992 American Association for the Advancement of Science). Abbreviations: *ADP* Adenosine diphosphate, *ATP* Adenosine tri-phosphate, *MH* Malignant hyperthermia

Clinical Manifestations

The first clinical sign can be any of the following: hypercapnia on capnogrophy that is uncorrected by minute volume changes, masseter spasm, or generalized hypertonia despite paralysis, peaked T waves in telemetry/electrocardiogram, and tachycardia with or without tachypnea [3, 10]. Sustained contraction of muscles results rapid progression to later manifestations such as rhabdomyolysis and severe metabolic and respiratory acidosis [3, 10]. Hyperthermia can develop in association with profuse sweating early and rapidly at the rate of 1 °C per every 5 min-1 hour (as high as 45 °C) or slowly (late manifestation) or is sometimes even absent [3, 10, 45, 46].

A recent study noted that when temperatures were not monitored closely, MH mortality increased to 30% [36, 47]. Continuous electronic core temperature monitoring is recommended [47]. Hyperkalemia leading to serious cardiac arrhythmias, including ventricular fibrillation, hemodynamic instability (hypotension or hypertension), and myoglobinuria, results in acute kidney injury and disseminated intravascular coagulation. Lab results often show CK elevation, metabolic (lactic) and hypercapnic acidosis, hyperkalemia, and myoglobinuria. Because all clinical manifestations may not be present in every patient, other differential diagnoses to be considered include neuroleptic malignant syndrome (NMS), thyroid storm, phaeochromocytoma, sepsis, inadequate anesthesia or ventilator or other equipment malfunction, serotonin syndrome, and intoxication with drugs of abuse such as cocaine, methamphetamine, ecstasy, bath salts, etc.

Treatment

The MHAUS have published guidelines for management of MH [48]. Immediate cessation of the surgical procedure, if possible, and discontinuation of triggering agent, prompt administration of intravenous (IV) dantrolene and fluid boluses, cooling (external or intravenous) to target <38.5 °C, hyperventilation, correction of severe metabolic acidosis (potentially intravenous bicarbonate for pH <7.2), and treatment of hyperkalemia are the corner stones of therapy [49, 50]. As this is labor and time intensive, additional assistance must be requested, especially for reconstituting stocked up dantrolene [49, 50]. Following a bolus IV dose of dantrolene at 2–2.5 mg/kg (actual body weight), further doses at 1 mg/kg body weight may need to be repeated every 4–6 hours, sometimes even exceeding >10 mg/kg of total dose until cardio-respiratory and hemodynamic abnormalities stabilize and dantrolene must be continued for at least 24 hours with patients being managed in an intensive care unit [48–50]. MHAUS recommends all hospital operating rooms and ambulatory surgical units using MH triggering agents to stock 36 vials of 20 mg each, just to be prepared for the worst-case scenario [48]. Although all the interventions should be timely, the timeline of dantrolene administration impacts the complication rate. US data reported an increase in complication rate by 1.6% when >30 minutes elapsed from first recognizable sign of MH to the first dantrolene dose, whereas a Canadian cohort reported an increase by >30% when time to first dose from the first sign of MH was delayed by >20 minutes [36, 51].

Management of arrhythmias using beta-blockers (esmolol) or amiodarone is recommended because co-administration of calcium channel blockers (for rate and hypertension control) with dantrolene may worsen intracellular hypercalcemia, hyperkalemia, and hypotension [10, 52, 53]. Following clinical stability and abatement of muscle rigidity for 24 hours, and subsidence of laboratory abnormalities such as declining CK, resolution of hyperkalemia, myoglobinuria, and acidosis, dantrolene dosing frequency can be decreased to every 8–12 hours. This is because recrudescence occurred in 20% of patients within 24 hours and those with a higher muscle mass and delayed time to first dantrolene dose were at the highest risk. [54]

Rhabdomyolysis and Hyperkalemia Without Malignant Hyperthermia

Succinylcholine can precipitate rhabdomyolysis in NMD by activating extrajunctional nicotinic acetylcholine receptors in denervated (causing widespread depolarization and hyperkalemia) or immobilized muscle or activation of an upregulated fetal γ receptors in certain NMD. [3, 55–58] Other predisposing factors include the following: severe hypokalemia from diarrhea, aldosteronism and diurectics, severe hypophosphatemia (alcoholism, ketoacidosis), myotoxic drugs and substances (steroids, statins/fibrates, cocaine/methamphetamine [hyperthermia and vasoconstriction]) can potentiate the occurrence of rhabdomyolysis [3, 59–61]. Laboratory abnormalities include elevated CK levels (>10,000 U/L), myoglobinuria, acute kidney injury (oliguric), hyperkalemia, and metabolic acidosis. Anti-hyperkalemic measures must be promptly instituted if electrocardiographic changes or severe hyperkalemia. Cessation of the offending agent, correcting/treating the underlying precipitating factor, aggressive intravenous fluid resuscitation, IV sodium bicarbonate to correct severe acidosis, and close monitoring are necessary.

Respiratory Complications

Patients affected with NMD are prone to post-anesthetic complications such as aspiration, hypoventilation, and acute respiratory distress. This is because of airway (pharynx, larynx) and respiratory muscle dysfunction as a sequelae of NMD as well as sleep apnea, scoliosis-associated restriction, and potentially malnutrition [62]. The vicious cycle of hypoventilation (from inspiratory muscle weakness) leading to atelectasis causing further increase in respiratory load of breathing which culminates as acute respiratory failure is frequently encountered in NMD treatment settings (Fig. 6.2) [4, 62, 63]. Similarly, inability to clear oral and/or respiratory secretions contributes to further atelectasis and coughing [64, 65]. Conditions especially implicated in aspiration due to bulbar muscle involvement include rapidly progressive NMD, spinal muscular atrophy, amyotrophic lateral sclerosis, and myasthenia gravis [1]. Mechanical ventilation itself, termed *ventilator induced diaphragm dysfuncion*, can exacerbate diaphragm weakness in NMD because of the adverse consequences of applying positive pressure to the diaphragm [66]. Nosocomial pneumonia and prolonged ventilatory requirements contribute to mortality and lead to tracheostomy for ventilator dependence. An extensive preoperative discussion on these risks versus the benefits of tracheostomy is always necessary [3]. Objective pre-operative pulmonary function assessment and training to use noninvasive mask ventilation (NIV) and cough assist devices may be vital in preventing these complications is the key factor to prevent such complications.

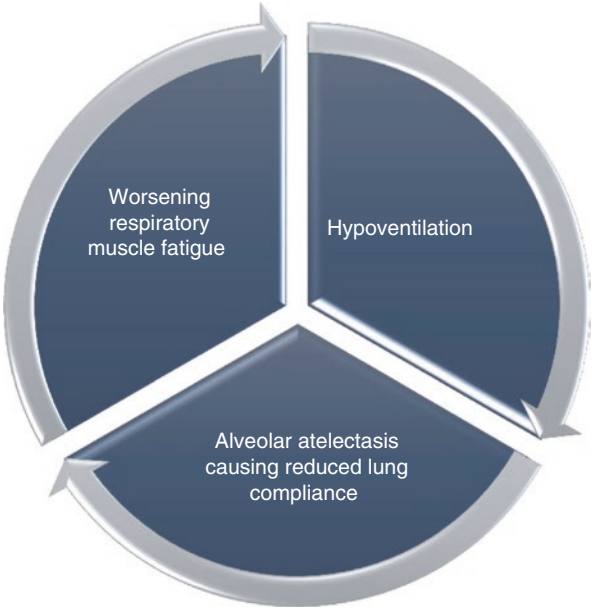

Fig. 6.2 Vicious circle of respiratory failure. (Reprinted with permission from Regunath et al. [4] © Springer International Publishing AG)

Cardiovascular Complications

Dysautonomia (Guillain-Barré syndrome, cervical myelopathy, amyloidosis, Shy-Drager syndrome, spinal muscular atrophy), cardiomyopathy, and conduction defects from muscular dystrophies and other inherited myopathies are the major chronic cardiovascular manifestations in patients with NMD [6, 10]. Inhalational anesthetics can trigger arrhythmias directly because they sensitize the cardiac muscle to catecholamines by interacting with cardiac muscle repolarizing K^+ channels mainly and to a lesser extent with calcium and sodium channels [67, 68]. Upregulation of acetylcholine receptors in denervated skeletal muscles can result in rapid development of hyperkalemia resulting in cardiac arrest, particularly triggered by succinylcholine [69]. Additionally, pulmonary hypertension may develop secondary to chronic hypoxia from worsening respiratory weakness and/or sleep apnea. Use of adequate intravenous fluid volume and appropriate inotropic agents for dysautonomia, anti-hyperkalemic measures and using beta-blockers or amiodarone and defibrillation are the treatment considerations as appropriate for those corresponding complications. Calcium channel blockers should be avoided in this patient population due to reasons mentioned in Table 6.2. Optimization of heart failure with diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or beta-blockers is also important to avoid heart failure exacerbations posing extubation issues following anesthesia and procedure completion [6].

Peri-operative considerations to Prevent Complications

Whenever possible, regional anesthesia should be preferred over general anesthesia (GA) [1, 3]. Amino-amide regional anesthetic agents (lidocaine, ropivacaine, and bupivacaine) are considered to be safe in NMD, but for rapidly progressive NMD, an accurate neurological assessment prior to regional anesthesia is essential to differentiate disease-related deficits and progression from those of regional anesthesia [8].

In neuropathic and neuromuscular junction disorders, inhalational anesthetic agents may be used, but for GA in myopathies, myotonias, and other NMD at high risk for MH, inhalational agents should be strictly avoided. National guidelines recommend flushing the anesthetic equipment of traces of volatile anesthetics prior to using them [70]. If GA is employed, total intravenous anesthesia using propofol, ketamine, etomidate, and dexmedetomidine and use of non-depolarizing paralytics such as rocuronium or vecuronium are recommended. In a Canadian population-based retrospective cohort study, the authors found that using these preferred agents for common inpatient and outpatient surgeries among patients with prior or suspected high risk for MH resulted in better outcomes when compared to control. These outcomes included a decrease in 30-day mortality, major post-operative complications, and readmissions [71].

During the procedure, continuous cardiac telemetry, pulse oximetry, and capnography should be monitored [3, 8]. Invasive arterial blood pressure monitoring should be considered for patients at risk for MH, dysautonomia, or unstable rhythms [1, 3, 6, 10]. Monitoring of core body temperature recommended as patients with NMD are susceptible to wide swings in temperatures from hypothermia due to impaired heat generation from weak/immobile muscles, associated dysautonomia, and hyperthermia of malignant hyperthermia or myotonic activity [3, 8, 36, 47]. When using paralytics, consideration should be given to monitoring neuromuscular function using train-of-four assessment [1, 10]. Following completion of the procedure, use of sugammadex for reversal of rocuronium- or vecuronium-induced paralysis may shorten the interval to reversal, avoiding lingering residual paralysis which poses risks of adverse respiratory complications [1, 10, 72].

Post-operative Considerations

Cardio-respiratory complications can occur following extubation [1]. Adequate clearance of respiratory secretions and ensuring oxygenation is within normal limits on room air prior to extubation is important, even if delaying extubation. Extubation to NIV is recommended for those with pre-operative FVC <50%, emphasizing the importance of pre-operative training with NIV and cough assist devices [1, 73]. Close monitoring in the intensive care unit must be considered in all patients with incomplete recovery from paralysis, severe congestive heart failure, ineffective

cough, and respiratory muscle weakness. Post-operative analgesia should be adequate especially in surgeries involving chest wall, cardiac, and/or thoracic spine to avoid post-operative hypoventilation from pain-related chest wall splinting [73].

Conclusion

Significant peri-operative complications related to anesthesia can occur in patients with NMD. A thorough pre-operative evaluation, judicious intra-operative management by careful use of non-halogenated sedatives, non-depolarizing paralytics, and intraoperative co-management of cardiac and metabolic conditions, followed by closely monitored post-operative care in a multi-disciplinary setting at centers equipped to provide such care, are essential to improve outcomes.

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Pregnancy and Neuromuscular Emergencies

7

Niraj Arora and Saurabh Kataria

Introduction

Neurologists are often expected to deal with a neuromuscular emergency in a pregnant female. It is often difficult to evaluate and treat these patients without proper understanding of the disease process. The physiologic changes during pregnancy, labor, and puerperium increase the maternal risk of neuromuscular complications. The purpose of the chapter is not to detail about every single neurologic disorder which could happen in pregnant females but to focus on commonly encountered neuromuscular emergencies confronted by the treating physician and how to practically deal with it. Most common disorders are listed below according to the location of injury:

1. Spinal cord: Trauma
2. Nerve and nerve roots: Guillain-Barre syndrome, compression-related nerve injuries
3. NM junction: Myasthenia gravis
4. Muscle: Inflammatory muscle disease

Traumatic Spinal Cord Injury (TSI)

Traumatic spinal cord injury (TSI) is defined as an insult to the spinal cord resulting in permanent or temporary change in the motor, sensory, or autonomic function. According to the National Spinal Cord Injury Statistical Center, approximately 22% of new SCIs occur in women of childbearing age [1]. Exact prevalence of SCI in

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pregnant patients is not known and there is paucity of literature of SCI in pregnancy. The mechanism of spinal cord injury in the order of frequency is motor vehicle collisions (42%), falls (27%), violence-related acts (15%), sports injuries (8%), and other causes (9%) [2, 3]. A poly-trauma pregnant patient poses a significant management challenge because of increased risk of fetal complications along with maternal comorbidities. It is crucial to triage these patients to the facility that is capable of managing these conditions with proper coordination with the primary obstetrician and the intensivist.

The costs associated with the management of adult patients with traumatic SCI are enormous, while the average life expectancy of a patient with TSI is lower than the general population [1].

Signs and Symptoms

The clinical examination of pregnant females with SCI should focuses on evaluation of not just the SCI but other associated trauma elsewhere in the body. The neurological exam should focus on motor and sensory examination along with checking for rectal tone and perianal sensations. A rough guide to determine the level of the injury can be done by checking for the associated myotomes and dermatomes (Table 7.1). Rectal tone is a sign of vital importance as it could differentiate complete SCI from incomplete SCI which has prognostic significance.

Table 7.1 The spinal motor and sensory roots with corresponding innervation

Spinal motor nerve root levels	Key spinal sensory nerve root levels
C1,2,3,4-Neck muscles	C2-Occipital protuberance
C3,4,5-Diaphragm	C3-Supraclavicular fossa
C4-Deltoid	C4-Top of acromioclavicular joint
C5-Biceps	C5-Lateral side of antecubital fossa
C6-Wrist extensors (extensor carpi radialis)	C6-Thumb
C7-Triceps, extensor digitorum	C7-Middle finger
C8- Flexor digitorum profundus	C8-Little finger
T1-Finger abduction, hand intrinsic muscles	T1-Medial side of antecubital fossa
T2-9-Intercostal muscles	T4-Nipple
T9-12-Abdominal muscles	T10-Umbilicus
L2-Hip flexors (iliopsoas, adductors)	T12-Inguinal ligament
L3-Knee extension (Quadriceps)	L2- Mid-anterior thigh
L4-Ankle dorsiflexion (tibialis anterior)	L3-Medial femoral condyle
L5- Extensor hallucis longus	L4-Medial malleolus
S1-Plantar flexion (gastrocnemius, soleus)	L5-Dorsum of foot at 3rd MTP joint
S2-Flexor digitorum, flexor hallucis	S1-Lateral heel
S2,3,4-Bladder, bowel sphincter	S2-Popliteal fossa in the mid-line
	S3-Ischial tuberosity
	S4,5-Perianal area

MTP metatarsophalangeal

The American Spinal Cord Injury Association (ASIA) Scale is a standardized tool to prognostic the SCI (www.asia-spinalinjury.org) [4–6].

Management

It is often challenging to manage an SCI during pregnancy. The management depends on the pregnancy trimester when the injury has happesned. It requires a multi-disciplinary approach in a tertiary care center under the expertise of obstetricians, surgeons, intensivist, and the rehabilitation team. Spinal immobilization, now called spinal motion restriction, plays a pivotal role in the pre-hospital management of any suspected SCI patients.

Some pregnant patients with penetrating injuries with or without cardiac arrest may have spinal cord injuries. Priorities in those cases are to maintain airway, breathing, and circulation (ABC) before considering spinal motion restriction. After hemodynamic stabilization, the goal is to decide the stability of the spine. Imaging studies plays an important role to localize the injury, and magnetic resonance imaging (MRI) is the preferred technique. The use of gadolinium should be limited in situations when benefits clearly out-weigh the risk [7]. Definitive treatment in the form of early surgical decompression (within 8–24 hours of injury) for unstable spine cases should be planned even if the complete SCI (ASIA-A) is present [8, 9]. Post-operatively, these patients should be managed in critical care units with focus on preventing secondary complications, such as venous thromboembolic disease, pressure ulcers, respiratory failure, and infections. The use of steroids for the management of SCI is no longer recommended and in fact it can cause side effects including death [10, 11].

Additional Considerations

If SCI occurs during first trimester of pregnancy, it is critical to prevent supine hypotension in the mother as it can cause hypoxia to the fetus during the spinal shock phase and increases the risk of miscarriage and fetal anomalies [12]. The pregnancy can still be carried till fetal maturity is attained before deciding on elective termination.

If SCI happens during the second or third trimester of pregnancy, one needs to be more watchful for the direct trauma to the uterus by compression or indirect trauma from flexion of the thoracic spine. Autonomic dysreflexia is the most dangerous feared complication in pregnant patients with SCI and could happen at any time during labor and delivery [13]. Analgesia during the delivery can potentially reduce the risk of autonomic dysreflexia [14, 15].

Regional anesthesia is generally preferred during labor. If general anesthesia is considered, rocuronium should be the muscle relaxant of choice. For pregnancy of more than 16 weeks, suxamethonium is the usual muscle relaxant for mandatory rapid sequence induction; however, there is a risk of hyperkalemia leading to cardiac arrest and death [16, 17].

Guillain-Barre Syndrome (GBS)

Introduction

GBS is an acute or subacute inflammatory disease of the peripheral nervous system which is either demyelinating or axonal with an annual global incidence of 1–2 per 100,000 person-years. The exact incidence of GBS in pregnancy in the United States is unknown, but one study found the incidence rate to be very low [18]. The rate is similar to any non-pregnant women [19, 20]. Studies from Sweden cohort utilizing national birth registry of live- and still-births estimated the rates of GBS to be 12 and 40 cases per million person-years, respectively, during pregnancy and post-partum (30 days) period [20]. Though the cost associated with management of GBS patients during pregnancy is not known, the disease has an economic burden of about 1.7 Billion dollars annually [21].

The disease can happen during any trimester of pregnancy and postpartum period but peak incidence during third trimester and first 2 weeks postpartum. Two-third of patients have a history of respiratory or gastrointestinal infections 1–3 weeks before the onset of symptoms [22]. Infections trigger an autoimmune reaction which has cross-reaction with the peripheral nerve antigen. Common infectious agents to consider are *Campylobacter jejuni* (*C. jejuni*), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and more recently Zika virus [23].

Symptoms and Signs

Clinical presentation of pregnant patients with GBS is the same as any adult patient with GBS. Typically, the disease could start with sensory symptoms like paresthesia in bilateral legs followed by motor symptoms in legs which gradually ascend to involve bilateral upper extremities and then cranial nerves [24]. Bulbar involvement in the form of dysphagia, shortness of breath, weak cough suggests severe injury. Reflexes are decreased or completely absent in most patients at presentation. Dysautonomia is quite common and manifests as variability in heart rate and blood pressure. Usually, there is absence of bowel or bladder symptoms [25]. Neuropathic or myopathic pain is reported by most patients [26]. Maximum disability is reached is about 2 weeks [27]. If there is rapid progression of symptoms within 24 hours of disease onset, alternative diagnosis should be considered. In atypical cases, disease could be unilateral and could involve all extremities simultaneously. There could be only motor or sensory with motor nerve involvement depending on the variants. The reader is referenced to Chap. 3 of this book for details about the symptoms and signs of GBS.

Management

Management of a pregnant patient with GBS does not differ much from a non-pregnant patient. However, pregnancy poses a risk of a very high mortality rate

(13%) due to respiratory complications. About 35% of pregnant women require ventilatory support during the course of the disease [22, 28]. Also, it should be noted that premature termination of pregnancy (i.e., delivery) has not been shown to improve the neurological condition of GBS [22, 29].

Electrophysiological studies can differentiate the subtypes of GBS into: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN) [30].

Plasmapheresis (PE) and intravenous immunoglobulin (IVIg) are the standard treatments so far for management of GBS in pregnancy. Treatment should be initiated early once a proper clinical diagnosis has been made. Safety and efficacy of IVIg is well established in pregnancy and should be the preferred treatment due to less complications than PE. PE is more beneficial when initiated within 7 days of disease onset but is still beneficial in patients treated up to 30 days after disease onset [31]. Plasmapheresis during pregnancy can cause coagulation abnormalities, hepatitis, maternal sepsis, and hemodynamic alterations which could precipitate uteroplacental insufficiency [32, 33].

Prompt attention to the identification and treatment of infections with appropriate antibiotics, prevention of venous thrombosis, pain management and counseling for psychosocial distress should be done when required [34]. Autonomic instability should be managed aggressively with labetalol as needed to preserve uteroplacental blood flow [35]. Neuritic pain and paresthesia can be managed with carbamazepine or opioids if needed [36].

GBS usually does not cause impairment in uterine contractions and so caesarean section and operative delivery should be sought only if indicated for obstetric reasons and normal vaginal delivery should be attempted first [37]. In one retrospective study of 47 patients of GBS during pregnancy, only two patients required C-section [34]. Normal fetal activity persists even if the mother is completely paralyzed. It suggests that immune-mediated phenomenon does not cross the placenta; however, there are case reports of infants born with hypotonia with mother having GBS which responded to IVIg.

There is an increased chance of preterm delivery (35%) in GBS complicating pregnancy though the perinatal survival rate is 95.7% [37]

Inflammatory Muscle Disease (IMD)

These are groups of heterogeneous muscle disease caused due to immune-mediated damage [38]. The most important to consider during pregnancy are polymyositis (PM) and dermatomyositis (DM). In general, they are uncommon acute, subacute, or chronic inflammatory muscle diseases which could present in pregnant females. Since there is a chance that autoimmune diseases flare up during pregnancy, IMD could be one of the presentations in a pregnant female with muscle aches and pain. The exact prevalence of PM/DM during pregnancy is not known, but prevalence in the general population is estimated to be 2.4–10.7 cases/100,000 people with females more affected than males and

more common in the reproductive age group. Endomysial auto-aggressive CD8 (+) T-cells and perivascular B-cells are responsible for immune-related damage in PM and DM, respectively [38, 39].

Successful pregnancy outcome is possible if the disease does not flare during pregnancy; however, there is a 50% chance of fetal loss in cases of exacerbation of disease [40]. Fetal growth could remain normal if the disease is in remission during pregnancy growth restriction with the disease in remission has been reported too [41]. There is high chance of perinatal morbidity and mortality and so care of these patients require careful supervision and high vigilance. Steroids are the first-line therapy for treatment of exacerbation during pregnancy. Other agents like IVIg and chemotherapeutic agents are considered second-line agents to control disease activity during flare-ups.

Compression-Related Nerve Injuries (Table 7.2)

Acute compression of nerve or nerve roots is very common in pregnancy or delivery. As a treating neurologist, one should be aware of common compression-related injuries that might present in the emergency room. Listing every possible nerve or root injury that could happen during pregnancy is beyond the scope of this chapter; however, common injuries are enlisted in the table.

Femoral neuropathy, obturator neuropathy, radial neuropathy, and postpartum foot drop are uncommon during pregnancy [42].

Postpartum foot drop can be due to injury at the level of nerve root, lumbosacral plexus, the sciatic nerve, or common peroneal nerve. Plexus injuries can happen during the second stage of labor due to compression by fetal head or using forceps during C-section [43]. Selective damage to the peroneal nerve fibers can happen due to compression by inappropriate leg positioning, squatting, or hyperflexion of knees with mother's hand on the lateral aspect of the leg are known risk factors [44, 42]. Epidural anesthesia increases the risk of common peroneal neuropathy. Electrodiagnostic studies help to differentiate the level of injury.

Cauda Equina Syndrome

Lumbar disc displacements leading to radicular symptoms are quite common in pregnancy and could happen in 50% of pregnant females. Most of these cases can be managed conservatively and some required surgical intervention like laminectomy or discectomy. However, about 2% cases of disc herniations present with severe neurologic deficits like significant leg weakness beyond the distribution of single nerve, sensory loss involving more than one dermatome, urinary retention, reduced anal tone [45, 46]. Urgent neurosurgical intervention should be sought to prevent permanent neurological damage and elective C-section should be performed [47].

Table 7.2 Neuropathies that could present during pregnancy [38]

Condition	Incidence	Timing	Symptoms/ signs	Risk factors	Treatment
Carpel tunnel syndrome	Most common upper extremity mononeuropathy	Most common in third trimester	Pain in the distribution of median nerve	Age >30years, nulliparous, third trimester	Splints, physical therapy, low-salt diet, local steroid injection if need, surgery: usually not required
Lumbosacral radiculopathy	Common	Any time during pregnancy	Pelvic-girdle pain (pain in sacroiliac joints and radiating to pubic symphysis or posterior thighs) or low back pain	Lumbar lordosis, direct pressure from uterus, laxed ligaments	Physical therapy, analgesics, trochanteric brace
Meralgia paresthetica (compression of lateral femoral cutaneous nerve of thigh)	Most common lower extremity mononeuropathy	Anytime during Pregnancy	Tingling, numbness or pain in lateral thigh unilateral (80%) or bilateral	Thigh flexion during labor or traction use during C-section	Usually recovers by itself after delivery, amitriptyline or local lidocaine patch, or injection
Postpartum foot drop	Uncommon	During labor and delivery	Inability to dorsiflex the foot	Multiple (see text)	Physical therapy or orthotics. Recovery in 3-6months or longer depending on type of injury (demyelinating versus axonal)
Bell's palsy	45 cases/100,000 population	Third trimester and puerperium	Mild weakness to total paralysis of one side of face	Associated with Preeclampsia and hypercoagulable state leading to thrombosis of vasa nervosum, immunocom-promised state due to pregnancy leading to increased risk of viral infection	Conservative. Steroid rarely required. Recovery in 3-6 months

Myasthenia Gravis (MG)

Introduction

MG is an autoimmune condition disorder of neuromuscular junction (NMJ) with high prevalence in women of childbearing age. It commonly affects women in the second or third decade of life. Estimated prevalence of MG during pregnancy is 1 in 20,000. The condition is characterized by weakness of skeletal muscles due to damage of NMJ by antibodies against acetylcholine receptors (AchRs) or other molecules on postsynaptic membranes [48, 49].

Symptoms and Signs

The cardinal feature of MG is fatigable weakness with repeated activity which improves with rest. Heat, infection, or any kind of stress could precipitate the weakness [50]. Typically, weakness involves specific muscle groups like bulbar, ocular, proximal muscles of extremities, or neck or respiratory muscles. However, the clinical severity of MG varies widely from only ocular involvement to generalized muscular weakness. There is improvement in clinical symptoms of MG during the second and third trimester (20–30% cases) related to immunosuppression during that phase. There is no difference in presentation in pregnant women compared to non-pregnant women.

Pregnancy has unpredictable effects on the symptoms of MG. Each pregnancy has its effect on MG symptoms and does not predict the course of subsequent pregnancies. Symptoms can occur in any trimester of pregnancy and early postpartum period; however, exacerbations are more common in the first trimester in about 33% cases [51, 52]. Involvement of respiratory muscles leading to respiratory insufficiency happens frequently in the first 3 weeks postpartum and requires close monitoring. Sudden and frequently severe exacerbations, including respiratory insufficiency, may occur in the first 3 weeks postpartum; therefore, close monitoring of MG signs and symptoms and timely adjustment of treatment is recommended during that time. This phenomenon is related to sudden drop in α-fetoprotein (AFP) concentration. Exacerbations during pregnancy could be related to underlying respiratory or urinary tract infections and should be promptly treated [53]. Coexisting autoimmune disorders are common in about 15% patients, and a thorough investigation should always be considered [54].

Please refer to Chap. 3 for additional details about the symptoms and signs of MG.

Management

Management of a pregnant female with new onset MG required a multi-team approach under the care of an obstetrician, neonatologist/pediatrician, and neurologist with active contribution by the patient and her family.

Table 7.3 Common drugs that can worsen myasthenia gravis

Drug class	Drug name
Anesthetic agents	Any neuromuscular blocking agents (succinyl choline, rocuronium, vecuronium)
Antibiotics	Aminoglycosides (gentamicin, neomycin, tobramycin) Fluoroquinolones (norfloxacin, levofloxacin) Macrolides (azithromycin, erythromycin)
Cardiovascular drugs	Beta-blockers (propranolol, metoprolol, atenolol) Procainamide Quinidine
Miscellaneous	Penicillamine Quinine Chloroquine, hydroxychloroquine Magnesium

Exacerbations of MG causing bulbar weakness or respiratory insufficiency during pregnancy should be treated aggressively to prevent fetal compromise. Plasmapheresis (PE) and intravenous immunoglobulin (IVIg) are safe and effective treatments. PE carries a theoretical risk of precipitating premature labor by removal of circulating hormones necessary for pregnancy as well as hypotension which could causes uteroplacental insufficiency. With IVIg, there is a risk of hypervolemia and hyper-viscosity syndrome which requires careful attention [55].

It is crucial to rule out thymoma, and thymectomy should be planned before pregnancy to avoid the additional risk of surgery during pregnancy. If detected during pregnancy, risk versus benefits of thymectomy surgery should be appropriately discussed.

Symptomatic treatment with pyridostigmine at doses less than 600 mg/day can be safely continued, but immunosuppressive medications should be discontinued to avoid potential adverse effects on the fetus. Treating physicians should be aware of drugs which could worsen myasthenia gravis and drugs which are potentially safe during pregnancy (Table 7.3).

There is no effect of MG on pregnancy although an increased risk of premature rupture of membranes does exist in myasthenic women due to unclear reasons [56, 57].

Vaginal delivery is recommended for women with MG as the disease does not affect the uterine smooth muscles. However, during the second stage of labor which involves the use of striated muscles, some assistance is generally required. C-section is reserved for obstetric indications as surgery causes stress which in itself could aggravate the symptoms of MG [53, 58–60].

During labor and delivery, epidural anesthesia is recommended as neuromuscular drugs can potentiate the effects of ACh receptor antibodies on the NMJ.

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Malignant Hyperthermia

8

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Introduction

Malignant hyperthermia (MH) is a rare life-threatening hypermetabolic disorder of skeletal muscle resulting from exposure to volatile anesthetic agents or depolarizing muscle relaxants. This hypermetabolic emergency is triggered by massive release of cytoplasmic calcium concentrations in the endoplasmic reticulum resulting in sequel of events which include hyperthermia, tachycardia, tachypnea, hypercapnia, acidosis, muscle rigidity, and even rhabdomyolysis. This chapter aims to highlight the basics of MH along with appropriate approach to symptomatic treatment and management of MH.

Epidemiology

The mortality rate associated with MH in early 1970s was 74%, but it has reduced significantly in the recent times with the introduction of dantrolene. Larach et al. conducted a study from 1986 to 2007 and determined the mortality rate in North America has reduced to 1.4% after the introduction of dantrolene [1].

The estimated incidence of MH with exposure to volatile anesthetic agents and depolarizing muscle relaxants is noted to be between 1:10,000 and 1:250,000 [2, 3]. Higher incidence of MH is seen in male than female population [4, 5]. MH is more often seen in younger population with mean age of 18.3 years [6].

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Genetics

MH is considered an autosomal dominant disorder and is most commonly associated with the mutation in the RYR1 receptor gene (ryanodine receptor gene). Genetic mutation in RYR1 gene are also associated with some RYR1-related myopathies like central core disease (CCD), centronuclear myopathy, multi-minicore disease, congenital fiber type disproportion (CFTD) which increase their susceptibility to MH [7]. Less common association of MH is also seen with genetic mutation in *CACNAI S* gene (calcium voltage-gated channel subunit alpha 1 S) and *STAC 3 gene* (SH3 and cysteine-rich domain 3). The *CACNAI S* gene encodes the alpha-one subunit of the dihydropyridine receptors (DHPR) of calcium channels. Mutations in this protein affect the residue, R1086, which is located in the large intracellular loop-connecting domains 3 and 4 and inhibits the RYR1 activity. As these channels activate RYR1, the mutation results in significant increase of intracellular Ca2+, thus causing muscle excitability [8, 9]. The genetic association of STAC 3 gene is seen more commonly in native American myopathy of North Carolina making this population more susceptible to MH [10].

Pathophysiology

The genetic mutations discussed above increases the susceptibility to MH on exposure to any triggering factor. The most common triggering factor for MH includes inhalation-halogenated anesthetic agents (ether, enflurane, isoflurane, halothane, sevoflurane, desflurane), and depolarizing muscle relaxants.

The exposure to these triggering factors results in rapid activation of the calcium channels which results in uncontrolled release of intracellular calcium ions in the sarcoplasmic reticulum of the skeletal muscle fiber resulting in sustained muscle contractions. These rapid contractions result in sudden depletion of the ATP (adenosine triphosphatase) which results in transition from aerobic to anaerobic metabolism. This hypermetabolic response further results in sequel of events leading to hyperthermia, tachycardia, tachypnea, hypercapnia, acidosis, muscle rigidity, and even rhabdomyolysis [11].

Clinical Presentation

One of the early presentations of MH results from increase in end tidal carbon dioxide (ETCO2). Significant increase in this ETCO2 results in hyperventilation and tachypnea. Exposure to the triggering factor like succinylcholine also results in masseter muscle spasm followed by significant muscle rigidity which results in a hypermetabolic state and rhabdomyolysis. The early symptoms seen in MH crisis after increase in ETCO2 include tachypnea, tachycardia, masseter spasm (after succinylcholine), hyperthermia, hyperhidrosis, muscle rigidity, hyperthermia, acute kidney injury, metabolic acidosis, respiratory acidosis. The lab marker seen in MH

Table 8.1 Inherited myopathies associated with malignant hyperthermia

Condition	Presentation	Inheritance
Central core myopathy [13]	Characterized by delay in motor development and lower limb muscle weakness associated with hypotonia in infancy	Autosomal dominant
Multi-minicore myopathy [14]	Characterized by hypotonia, delay in motor development, muscle weakness mainly in lower limbs, and musculoskeletal abnormalities	Autosomal recessive
King-Denborough syndrome [14]	Characterized by hypotonia at birth, mild proximal muscle weakness, delay in motor development, joint hyperextensibility, and dysmorphic facial features including ptosis, low-set ears and high arched palate, micrognathia, malar hypoplasia, hypertelorism, along with palmar simian line, pectus excavatum, winging of scapulae, lumbar lordosis, and thoracic scoliosis	Autosomal recessive
Native American myopathy [15]	Most commonly seen in Lumbee Indians of North Carolina Characterized by congenital weakness, arthrogryposis, cleft palate, short stature, talipes deformities, and kyphoscoliosis *STAC3* mutations predispose them to develop MH provoked by anesthesia, therefore depolarizing muscle relaxants and volatile anesthetics must be avoided.	Autosomal recessive

include hyperkalemia, elevated CK, elevated myoglobulin level, hyperthermia with increase in body temp 1°C every 5 min [12]. This clinical presentation is not typical of MH; hence, other differentials such as neuroleptic malignant syndrome, heat stroke, drug toxicity, chromaffin tumors, sepsis should be kept as differentials as well.

Inherited Myopathy Related to Malignant Hyperthermia

Various inherited myopathies have genetic predisposition to RYR 1, *CACNAI S*, and *STAC3* gene which can further increase their susceptibility to MH. Table 8.1 includes a brief summary of the most common inherited myopathies like central core myopathy, multi-minicore myopathy, King-Denborough syndrome, Native American Myopathy related to malignant hyperthermia.

Diagnostic Criteria

Clinical Grading System

Larach et al. have introduced a clinical grading scale for initial diagnosis of MH, which includes six categories of the symptoms mainly muscle rigidity, muscle breakdown, respiratory acidosis, temperature, cardiac involvement, and other variable factors (Table 8.2) [16]. Each of these components are then differentially graded in scale and MH likelihood and MH rank are calculated accordingly (Table 8.3).

Table 8.2 Clinical grading scale for malignant hyperthermia

Clinical process	Indicator	Points
Rigidity	Generalized muscular rigidity without shivering due to hyperthermia during or immediately following emergence from inhalational anesthesia	15 points
	Spasm of the masseter muscles shortly after succinylcholine administration	15 points
Muscle breakdown	CK >20,000 IU after anesthesia with succinylcholine	15 points
	CK >10,000 IU after anesthesia without succinylcholine	15 points
	Cola-colored urine in perioperative period	10 points
	Urine myoglobin >60 mcg/L	5 points
	Serum myoglobin >170 mcg/L	5 points
	Serum K >6 meq/L without renal failure	3 points
Respiratory acidosis	Controlled ventilation PETCO2 >55	15 points
	Controlled ventilation PaCO2 >60	15 points
	Spontaneous ventilation PETCO2 >60	15 points
	Spontaneous ventilation PaCO2 >65	15 points
	Inappropriate hypercarbia (in anesthesiologist judgment)	15 points
	Inappropriate tachypnea (in anesthesiologist judgment)	10 points
Temperature increase	Abnormal rapid rise in temperature (in anesthesiologist judgment)	15 points
	Inappropriate perioperative rise in temperature >38.8 °C (in anesthesiologist judgment)	10 points
Cardiac involvement	Inappropriate sinus tachycardia (in anesthesiologist judgment)	3 points
	Ventricular tachycardia or ventricular fibrillation (in anesthesiologist judgment)	3 points
Others	Arterial pH >7.25	10 points
	Rapid reversal of MH signs with dantrolene	5 points
	Positive family history along with positive personal anesthetic history without elevated resting serum CK levels	10 points
	Elevated resting serum CK in patient with positive family history	10 points

Table 8.3 Correlation between total criteria point and MH rank and MH likelihood

Total points	MH rank	MH likelihood
0 points	1	MH likelihood is *almost never*
3–9 points	2	MH likelihood is *unlikely*
10–19 points	3	MH likelihood is *somewhat less than likely*
20–34 points	4	MH likelihood is *somewhat greater than likely*
35–49 points	5	MH likelihood is *very likely*
50–108 points	6	MH likelihood is *almost certain*

Muscle Susceptibility Test

The gold standard diagnostic test to determine the susceptibility to MH is In Vivo Contracture Test (IVCT) also known as Caffeine-Halothane Contracture Test (CHCT) [17, 18]. Similar concept is used in both the test; a muscle biopsy is taken and subsequently observed for contraction in the muscle after treating it with halothane or caffeine. The only difference between the two tests is the use of different concentration and modes of testing agents. The IVCT is developed by the European Malignant Hyperthermia Group (EMHG) and the CHCT is developed by the North American Malignant Hyperthermia Group (NAMHG). An individual is considered positive for susceptibility when both caffeine and halothane test are positive (MHS –Malignant Hyperthermia Susceptibility) and unsusceptible when both tests are negative. If one of the tests is positive, individuals are diagnosed as either MHS(h) or MHS(c) for halothane or caffeine, respectively. The NAHMG protocol carries a specificity of 78% and sensitivity of 97%, and the EMHG protocol has a sensitivity of 99% and specificity of 94% [19, 20].

Genetic testing can be used as another mode of testing to determine the susceptibility to MH. There are more than 40 different variants of RYR1 genes which are responsible for causing central core disease and malignant hyperthermia. These variants can be determined by the parallel sequencing or next-generation sequencing (NGS) which is an accurate and cost-effective approach as compared to other traditional DNA sequencing techniques [21, 22].

Management

Dantrolene is the only drug so far effective in the management of MH. Dantrolene potentiates it action by inhibiting the DHPR (dihydropyridine) on ryanodine receptor, thereby inhibiting the release of intracellular calcium ions [23]. The dose of dantrolene can be repeated every 5 min until when the max dose of 10 mg/kg/24 hr. is reached or when the patient has stabilized. Dantrolene is available as Dantrium® in the dose of 20 mg and Ryanodex®, the newer formulation which is available in 250 mg ampule form. This new formulation requires lesser preparation time, less

Step wise approach to management of MH

1. Stop the triggering agent
2. Increase the minute ventilation by providing 100% oxygen flow to reduce ETCO2
3. Administer dantrolene (2.5 mg/kg every 10-15 minutes until symptoms resolve)
4. For hyperthermia administer cool iv fluids; ice packs; cold gastric lavage
5. For arrythmia: manage with antiarrhythmics amiodarone; lidocaine
6. For hyperkalemia manage with calcium gluconate, iv insulin and dextrose
7. Monitor blood gases, electrolytes, creatine kinase, urine and blood for myoglobin
8. Patient should be accessed for next 48-72hour in intensive care settings for reoccurrence of symptoms.

Fig. 8.1 Step-wise approach in the management of MH in ICU setting

fluid vials, and has faster administration rate as compared to other forms of dantrolene like Dantrium® and Revonto® [24]. It is crucial to monitor the patient for next 48–72 hour in ICU for reoccurrence of symptoms after the administration of the drug. If the patient does not stabilize with the administration of dantrolene, other possible differentials should be excluded like sepsis, intracranial hemorrhage, baclofen withdrawal, chromaffin tumor, drug toxicity, and neuroleptic malignant syndrome [25].

Apart from administration of dantrolene, symptomatic treatment is equally essential and should be initiated as soon as possible. The first step in the management is to discontinue the possible triggering agent. Hyperthermia can be managed by cold compresses, cold intravenous fluids, and if required cold gastric lavages. The disorders of electrolyte imbalance and acid base disorders should be managed accordingly in order to prevent acute kidney injury. The Figure 8.1 gives the step-wise approach in the management of patient with MH.

Conclusion

Malignant hyperthermia is a rare life-threatening pharmacogenetic disorder of the skeletal muscle. Even though the introduction of dantrolene has significantly reduced the mortality rate of MH in United States, it still remains a significant risk factor for genetically susceptible individuals exposed to triggering factors. The Malignant Hyperthermia association of United States (MGAUS) makes every effort to provide with structured management protocols, information updates, detailed task cards regarding latest updates in the management strategy of MH, and creating more awareness of the disorder. It is crucial for all clinicians to recognize early signs and symptoms of MH presentation on exposure to triggering factors, in order to initiate prompt medical management and prevent the life-threatening sequalae of this disorder.

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Pediatric Neuromuscular Emergencies and Urgencies

9

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Introduction

Patients with acute weakness as a primary concern due to neuromuscular disorders often present to the emergency department (ED) for an evaluation. It should always be treated as a medical emergency and expedient diagnosis is crucial. A systematic and timely approach to diagnosis hinges primarily on meticulous, organized history taking, and neurological examination. The acute weakness can present with either paresis or paralysis resulting from lesions at any level in the central or peripheral nervous system. The lesion could be anywhere from the cerebral cortex, spinal cord, neuromuscular junction, or muscle fiber itself. The history should focus on onset of symptoms, progression, distribution of weakness, pure motor, sensory or mixed symptoms, involvement of cranial nerves, autonomic nervous system, bowel and bladder disturbances. Table 9.1 illustrates the affected locations, clinical features, and examples of acute weakness encountered in the pediatric population. However, the chapter includes only common causes of neuromuscular emergencies in the pediatric population.

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Table 9.1 : Affected location, clinical features, and common disease encountered

Location of lesion	Clinical features	Examples
Central nervous system	Focal weakness, sensory deficits or cranial nerve abnormality, hyper-reflexia, and extensor plantar response	Stroke, trauma, tumor
Spinal cord	Symmetric paralysis or quadriparesis, bladder or bowel sphincter disturbance with sparing of bulbar muscles Initial areflexia below lesion Loss of sphincter tone	Transverse myelitis, infarction, tumor, demyelination, myelopathy
Anterior horn cell	Symmetric weakness and normal or depressed deep tendon reflexes	*Poliomyelitis, west Nile-related disease,* spinal muscular atrophy
Neuromuscular junction	Fatigable weakness, bulbar symptoms, ptosis	*Myasthenia gravis*, Lambert-Eaton syndrome, *botulism*
Peripheral nerve	Distal more than a proximal weakness, reduced or absent reflex, facial or other cranial nerves may be involved, often accompanied with preceding illness	*Tick-borne paralysis, acute inflammatory demyelinating neuropathy(AIDP)*
Muscle	Proximal more than a distal weakness, preserved sensation and reflexes, may be associated with rash and muscle pain	Myositis, muscular dystrophy

Disorders of Anterior Horn Cells

Diseases affecting anterior horn cells may present at any age from infancy to the elderly. However, in early childhood and adolescence, disease often restricted to anterior horn cells causes pure motor weakness. Other distinguishing features in the adult and elderly population are involvement of other systems like upper motor neuron, bulbar symptoms. Infection is one of the major causes for anterior horn cells disorders in the pediatric population [1].

Poliomyelitis

Introduction

Poliomyelitis is an infectious disease caused by the poliovirus; it is an *Enterovirus* and belongs to the Picornaviridae family. It was endemic in the United States and Europe until the 1950s. It is uncommon in the United States due to inactivated poliovirus Salk vaccine in 1955, and then the attenuated oral poliovirus vaccine (Sabine) in 1963. However, it is still endemic in developing countries such as Pakistan, Afghanistan, and Nigeria [2]. It was estimated that up to 20 million people worldwide were affected worldwide from sequelae of poliomyelitis. If the patients presents with new neurological symptoms after decades of polio infection, known as post poliomyelitis syndrome (PPS). PPS is more common in polio

survivors, and up to 25–50% of patients will experience the symptoms; however, the cause remains unknown [3].

Clinical Presentation

Most common route of transmission is fecal oral contamination. The virus targets anterior horn cells in the spinal cord or brain stem. Patients often presents with an acute asymmetric flaccid muscle paralysis with depressed reflex and respiratory failure requiring ventilatory support due to medullary and respiratory muscle involvement and clinically mimics as an acute inflammatory demyelinating polyneuropathy (AIDP). Viruses such as rabies, coxsackievirus, and echovirus can also present similarly. The key feature which distinguishes it from other enteroviral infection is prodromal syndrome such as mild respiratory or gastrointestinal illness, often associated with myalgia followed by rapidly progressive weakness which is often asymmetric [4]. Patients with PPS present with three most common symptoms such as fatigue, weakness, and pain. Fatigue is the most common problem, and symptoms include post-exercise exhaustion following physical activity, poor sleep, and impaired concentration. Weakness often starts initially in affected limits, but it can affect other limbs as well. Children often complain of myalgia, arthralgia, deep burning, and cramping pain [5].

Diagnosis

The diagnosis is based on isolation of the virus by polymerase chain reaction (PCR) in stool, cerebrospinal fluid (CSF), saliva, and blood. One way to distinguish AIDP from poliomyelitis based on CSF studies is that in AIDP there is elevated white cell count and protein. In earlier stages of poliomyelitis, patients may have normal CSF studies.

Treatment

The clinical course is variable and often has an incomplete recovery. Children with respiratory and bulbar muscle paralysis require mechanical support, aspiration precautions. Treatment is entirely symptomatic [2]. Recent studies show there is a role of IVIG in PPS as it shows reduction in pain and improvement in quality of life. However, it failed to show an improvement with muscle strength and fatigue [6, 7].

Acute Flaccid Paralysis (AFP)

Introduction

Acute flaccid paralysis (AFP) specially affects the anterior horn cells in spinal cord results in weakness and flaccid paralysis of affected muscle or limb often following a viral illness. It affects both the adult and pediatric population, with male predominance also having a strong predilection for upper limbs [8]. It was first reported in 2014 and a threefold increase in incidence in 2018 [9]. The projected incidence of AFP was 0.32 cases/100000 population/year with a median age of 6 years old [10]. The cause remains unknown; however, it was thought to be due to non-polio

enteroviral infection. There was an increased incidence of AFP in US children which has been linked to enterovirus-D68 (EV-D68) [11] and closely resembles the syndrome caused in other countries by enterovirus-71 (EV-71) [12].

Clinical Presentation

The clinical presentation is divided into three different stages: (1) prodromal phase, (2) neurological injury, and (3) convalescent phase. The prodromal phase includes symptoms of upper respiratory infection, gastrointestinal symptoms, rash, lymphadenopathy, and headache [13]. Prodromal symptoms usually resolve before the acute neurological injury begins. The neurological injury is often acute and rapidly progressive; symptoms include myalgia, flaccid weakness, and depressed reflexes, sometimes involving entire neuraxis results in encephalo radiculitis [13–15]. Affected limbs result in atrophy. Currently the Center for Disease and Control (CDC) proposed a definitive and probable diagnostic criterion based on clinical features [16].

Diagnosis

The diagnosis is based on clinical presentation and presence of T2 hyperintensity in gray matter of the spinal cord which spans at least three levels [14]. Cerebrospinal fluid analysis shows elevated protein and lymphocytic predominance which can also be seen in patients with other viral infections such as poliomyelitis, west Nile virus, and HIV [17, 18]. The virus is isolated by either through stool or oropharynx and confirmed with real-time polymerized chain reaction (PCR) [16]. Electrodiagnostic studies may not be useful to make a definitive diagnosis, and findings are consistent with asymmetric motor neuronopathy/polyradiculopathy [13].

Treatment

There is no definitive treatment . Other treatments such as IV methylprednisolone, IVIG, and plasmapheresis did not show any short-term improvement with symptoms. Close monitoring of bulbar and respiratory function are the most important interventions. It is advised to keep patients on nothing per mouth (NPO) to prevent aspiration. Frequent monitoring of negative inspiratory force (NIF) and vital capacity to assess the need for intubation and extubation as well [13].

Outcome

A small study by Nelson et al. followed 11 children over 1 year, and found that 90% continued to have motor deficits at follow-up regardless of medical treatment [19]. Long-term recovery remains unknown.

Disorders of Peripheral Nerves

Guillain-Barre Syndrome (GBS)

GBS is the most common cause of acute flaccid paralysis in children and infants [20]. The incidence among the pediatric age group is estimated to be between 0.4

and 1.3 per 100,000 per year [21]. The incidence increases with every year of age at a rate of about 0.6 per 100,000 per year in children [22]. It is of diagnostic importance to note that GBS is uncommon in children under the age of 2 [21]. Previously GBS was considered to be a homogenous disorder referring to acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in which the immune-mediated damage only targets the myelin sheath [22]. It is now defined as a spectrum of immune-mediated post-infectious polyradiculoneuropathy with motor/ sensorimotor components [23]. There are two main subtypes: AIDP in which myelin is targeted and AMAN (acute motor axonal neuropathy) in which the axolemma is targeted (resulting in axonal injury) [22]. AIDP is the most common variant in North America and Europe constituting 85–90% of the cases [24]. There are many rare variants of GBS; among them, the most common one is Miller Fisher syndrome classically present with the triad of ophthalmoplegia, areflexia, and ataxia with subtle or no weakness.

History

Patients often present with acute onset of symmetrical progressive weakness with a history of antecedent respiratory or diarrheal illness, surgical procedure, and immunizations approximately 1–6 weeks prior to the presentation [25–27]. There is ascending weakness, predominantly in the lower extremities, with the disease process reaching its nadir at approximately the fourth week [27]. The gait abnormalities may include inability to walk, wide-based gait, climbing stairs, and difficulty running.

Sensory symptoms such as tingling dysesthesias and paresthesias may also be present. Pain is also a common complaint among the pediatric population, commonly localized to the shoulder back or posterior thigh [21] . Bilateral facial weakness may also be reported, as the cranial nerve is involved in 50% of cases. Patients with autonomic involvement may also have a history of bladder dysfunction, paralytic ileus, tachycardia, and orthostatic hypotension [21]. The diagnostic criteria outlined by Ashbury and Cornblath are a useful guide to aid in targeted history taking and examination [28].

Physical Findings

Symmetrical weakness is more prominent in the lower extremities. Deep tendon reflexes are usually absent or diminished in both upper and lower extremities. Most often patients will have a positive straight leg test which is probably due to inflammation of the proximal nerve root. Cranial nerve involvement is common, and facial diplegia and Bell's palsy should be looked for variants of GBS [21]. Signs of bulbar symptoms are seen in 25% of patients with many patients presenting with dysphagia or drooling often seen in patients with Miller Fisher variant [29]. Patients may also show signs of autonomic dysfunction including orthostatic hypotension, tachycardia, and hypotension or hypertension [21].

Diagnosis

Diagnosis of GBS is based upon clinical history and physical examination findings. Treatment should not be delayed for additional workup and definitive diagnosis.

The diagnostic tests can be used to confirm diagnosis, especially in cases of atypical presentation. The two most helpful confirmation studies are cerebrospinal fluid (CSF) analysis and nerve conduction studies (NCS). CSF analysis classically shows an elevated protein count with a normal cell count (<10 cells per mm3, all cells being leukocytes). Protein counts generally reach their nadir within 4–6 weeks of illness and begin to rise from the day of onset and will show a reasonable elevation within a week. Note that a normal protein count does not definitively rule out GBS, while cell counts higher than 50 cells per mm^3 should reconsider the diagnosis of GBS [21]. Patients elevated with white cells (>10cells per mm^3) along with elevated protein should have strong suspicion for infectious etiology, especially affecting anterior horn cells in the spinal cord.

Electrodiagnostic studies may remain normal during initial stages of disease. As the disease progresses, it reveals features of demyelination which includes prolonged distal motor, H and F wave latency, reduced conduction velocity, and other features like conduction block and temporal dispersion seen in later stages [29]. In AMAN, AMSAN, and MFS, there will be no signs of demyelination; however, there will be reduced amplitude of compound nerve potentials.

In cases with rapid onset of weakness and dysautonomia, GBS may be confused with acute spinal cord lesions such as transverse myelitis, compressive myelopathy, etc. Clinically lack of spinal level on sensory modalities such as pin prick, vibration sensation favors GBS, and additionally a spinal MRI can be used to differentiate the two. MRI findings in GBS will classically be anterior spinal nerve root enhancement in the terminal spinal cord level. This enhancement indicates that there has been a breakdown at the blood-nerve barrier which could be indicative of the inflammatory process.

Mimickers of GBS

Other conditions can present with similar clinical features which include acute intermittent porphyria, paraneoplastic, post-diphtheritic, certain toxic neuropathies such as arsenic or thallium, and chemotherapeutic agents such as vinca alkaloids.

Morbidity

There are two main causes for morbidity in GBS: *respiratory failure* and *dysautonomia*. Because of the risk of fatal complications, children with GBS are often shifted to the pediatric intensive care unit (PICU) for monitoring [30]. Patients most at risk for respiratory failure include those that develop rapidly progressing weakness involving the upper extremities, those with bulbar symptoms, facial nerve involvement, as well as autonomic instability [31]. Pulse oximetry should not be depended on to gauge respiratory sufficiency necessitating a baseline FVC or negative inspiratory force measurement. The risk of respiratory failure and indication for intubation can be assessed using lung capacities outlined in the table below.

Assessing need for endotracheal intubation [32]
1. FVC <20 ml/KG
2. MIP <30 cm H20
3. MEP <40 cm H20
Worsening of respiratory status is more likely in patients with a greater than 30% drop in any of these parameters.

A study done by Lawn et al. found that a little less than half the patients with a rapid decline in vital capacity within the first 24 hours of admission required intubation [31]. Another prospective study following the course of GBS in 95 pediatric patients (primarily suffering from the AIDP subtype) found that 13% of patients required mechanical ventilation and 18% were thought to have respiratory compromise.

The study also observed that 51% of the patients had symptoms of dysautonomia, the second most common cause for fatality in pediatric GBS [33]. Autonomic instability can manifest as cardiac dysrhythmias, orthostatic hypotension, hypertension, paralytic ileus, urinary retention, altered sweating, or acral cyanosis [21].

Treatment

Treatment of GBS requires a two-pronged approach: *supportive* and *specific care*.

Supportive Care

Supportive care includes DVT prophylaxis and frequent turning to prevent decubitus ulcers and pressure neuropathies in non-ambulatory patients, respiratory support, and intubation when indicated, and prevention of atelectasis and aspiration. Rehabilitation to prevent contractures, skin breakdown, and restore function should be initiated as soon as a patient is admitted for GBS [21].

Specific Care

Specific treatment for GBS is aimed at hastening recovery and includes plasma exchange (PE) to decrease autoantibodies and intravenous immunoglobulin to reduce levels of proinflammatory cytokines. The American Academy of Neurology has outlined treatment guidelines for GBS in adults which have been extrapolated to treatment of the pediatric population as there is a lack of randomized controlled treatment trials in children currently. The recommendation for non-ambulatory patients is plasma exchange within 4 weeks of symptom onset and IVIG within 2 weeks of symptom onset. In ambulatory patients, plasma exchange may be considered within 2 weeks of symptoms. There was no evidence of additional benefit in using steroids, additional courses, or IVIG and PE together [34]. Due to difficulties in performing PE in children, the treatment of choice for pediatric GBS has become IVIG. Recommended dosing is 2 g/kg total of IVIG in equally divided daily doses over 2–5 days. For children who are able to walk or who have reached the plateau phase of the disease, supportive treatment alone is recommended. This is however to be decided on a case-by-case basis as many pediatric neurologists will recommend IVIG treatment in children regardless of ambulatory status, and particularly in those with bulbar symptoms or respiratory involvement [5]. Adverse effects of IVIG treatment in children are outlined in the American Academy of Pediatrics 2012 report of the Committee on Infectious Diseases, and include anaphylactoid reactions, renal dysfunction, thrombotic events, and renal failure [23].

Plasma exchange if chosen should be given as one plasma volume exchange alternate days, for a total of up to 5–7 courses. Adverse events associated with PE include acquired infections from impure blood products, hypotension, thrombosis, and arrhythmias [79].

Prognosis

In contrast with GBS in adults in whom morbidity and mortality are quite high, the prognosis for pediatric GBS is very good. A multicenter study conducted on the course of childhood GBS observed recovery and improvement in weakness at a median of 11 days, return of unaided ambulation in a median of 43 days, and no residual symptoms in 75% of patients in a median of 106 days [33]. Another long-term study following 47 cases of pediatric GBS found that 46% had some residual neurologic abnormalities, of which 27% had decreased or absent deep tendon reflexes and 15% had sensory disturbances. Twenty-three percent had mild residual weakness in at least one muscle group [35].

Tick Paralysis

Though tick-related paralysis is uncommon in the United States, it is primarily seen in the pediatric population in Southeastern, Rocky Mountain, and Pacific Northwest regions of the United States [36]. Symptoms of tick paralysis may be confused for GBS and vice versa as both diseases cause ascending symmetric weakness. A thorough history and examination is required to rule out tick paralysis and remove the tick in a timely manner. Tick paralysis is caused by the attachment and feeding of a gravid female tick followed by release of neurotoxin into the patient's bloodstream. The most common species of tick to cause illness in North America are *D. variabilis* (American dog tick) and *Dermacentor andersoni* (Rocky Mountain wood tick), as well as *Amblyomma americanum* (Lone Star tick) and *Ixodes scapularis* (deer tick) [36–38]. Pathogenesis is somewhat similar to botulinum, involving failure of acetylcholine release from the presynaptic junction. The *Dermacentor* species produces a toxin called ixobotoxin that is hypothesized to affect sodium flux across axonal membranes and hence inhibit acetylcholine release in response to an evoked potential [39].

Clinical Features

Typically tick paralysis is seen in children who have been in endemic areas from April to June and are younger than 10 years. The patients and parents may or may not be able to give history of a tick bite. If history of tick bite is elicited, it is important to note that symptoms often begin within 5–7 days of the female tick attaching itself to the patient [38]. History of an ascending symmetrical paralysis that begins with lower limb weakness will be present. Ascending weakness may be noticed as clumsiness or ataxia and is due to either the early effects of the toxin on the cerebellum or lower limb weakness [38, 40]. Within hours to a day, the weakness progresses to include the trunk and upper extremities.

Bulbar symptoms such as ophthalmoplegia, facial paralysis, dysarthria, and dysphagia may be present, though this is often seen late in the course of the

disease [37, 38, 41]. There is however a lot of variability in the presentation of tick paralysis, and cases of acute bulbar palsy in the absence of advanced motor weakness have been reported [39].

Physical Examination

Patients with tick paralysis will exhibit the classic symmetric ascending paralysis. Deep tendon reflexes are also significantly reduced or absent, also in an ascending order [39]. Late-stage tick paralysis eventually involves the cranial nerves, observed as facial nerve or bulbar involvement. Ophthalmoplegia may be present as minimal pupil reaction or as limited extraocular movement. Respiratory function should also be assessed as late-stage disease can lead to respiratory muscle weakness, progressive hypoventilation, lethargy, coma, and death [38].

Diagnosis

Tick paralysis is diagnosed by visualizing the tick along with the supporting history. Ticks favor feeding behind the ear and are often found attached to the scalp there. A careful examination of all body surfaces and crevices should be conducted, with particular focus on the scalp, axilla, and pubic regions where ticks are often missed [39]. Nerve conduction studies demonstrate low-amplitude action compound muscle potentials with normal conduction velocities, normal sensation, and normal response to repetitive stimulation [42].

Morbidity

Fatality of tick paralysis is related to respiratory compromise. Mortality due to respiratory failure in patients with undiagnosed tick paralysis is around 10% [30]. If there is a risk of respiratory failure (significant respiratory muscle weakness/bulbar symptoms), the patient should be monitored in the ICU and intubated if necessary. Respiratory support may be required after tick removal as well. Other possible complications include myositis and myocarditis [42].

Treatment

Ascending tick paralysis resolves with removal of the offending tick/ticks using tweezers or forceps to grasp the head of the tick and pull with slow steady pressure. Care should be taken not to leave the head of the tick in the skin. Technique is important, as gripping the tick too forcefully can lead to release of a large dose of toxin into the child's bloodstream [39]. Respiratory support in patients with hypoventilation may be required for greater than a week [42].

Prognosis

Tick paralysis caused by North American species resolves quickly after removal of the tick. Improvement in weakness is seen within hours, and complete resolution is generally seen within 24–36 hours [37].

Disorders of Neuromuscular Junction

Myasthenia Gravis

Background

Myasthenia gravis (MG) is an autoimmune disorder in which the neuromuscular transmission is impaired due to the presence of antibodies against structural components in the muscle membrane. This leads to disruption of impulse transmission at the neuromuscular junction, eventually causing fatigable weakness. There is a worldwide increase in incidence and prevalence due to more widespread availability of antibody testing and the better understanding of clinical presentation [43]. The estimated prevalence is 40–180 per 100,000 people with an annual incidence of 4–12 per 100,000 people [44]. Juvenile myasthenia gravis is most commonly seen in patients of East Asian origin and half of the cases have an onset before the age of 15 and is restricted to ocular muscle only.

Roughly around 80% of MG cases are caused by anti-acetylcholine receptor antibodies (ACHRab). There are other less common variants in involving antibodies targeting other postsynaptic neuromuscular antigens including muscle-specific kinase (MUSK), lipoprotein-related protein-4 (LRP4), or agrin in the postsynaptic membrane at the neuromuscular junction [44, 45]. Thymomas are rarely seen in juvenile myasthenia gravis (the most common pediatric variant of MG) and are more commonly seen in peri- and post-pubertal MG caused by AchR antibody [46].

Clinical Presentation

The most common presenting symptom in children is ptosis with up to 90% of children presenting with signs of extraocular muscle weakness [47, 48] . Other associated ocular symptoms include diplopia, unilateral or asymmetric ophthalmoplegia, and strabismus (though they may only be revealed on sustained upward gaze) [47, 48]. Approximately, 10–15% of patients will present with purely extraocular muscle weakness termed ocular myasthenia gravis [49, 50].

Patients may also present with dysphagia (ask for any sudden weight loss or refusal to eat), drooling, or dysphonia indicating bulbar involvement. Limb weakness may be present more so in the proximal extremities and often manifests as difficulty climbing stairs [47]. Children may also present with aspiration pneumonia due to bulbar weakness.

Weakness will be characteristically fluctuating, worsening on exertion, and improving on rest. History of worsening of symptoms as the day progresses should be noted. Patients previously diagnosed with MG may present with these symptoms if their medication is being tapered, or due to factors that aggravate MG including systemic illness, menstrual cycles, hot temperatures, and hypo- or hyperthyroidism [51]. Respiratory distress is a key clinical sign that should be looked for as it indicates the patient is in “myasthenic crisis.” These patients may also present with weakness and secretions similar to cholinergic crisis (in treated patients) and both should be differentiated as the treatment course varies.

Important Variants in the Pediatric Population

While this chapter focuses on the presentation and treatment of Juvenile myasthenia gravis, there are two other pediatric subtypes that should be noted.

Neonatal Myasthenia Gravis

The incidence occurs anywhere between 5% and 30% of children born to mothers with autoimmune MG [52]. In this subtype, there is a transfer of maternal autoantibodies to the infant. Children will present soon after birth with hypotonia, respiratory distress, poor feeding, weak facial expressions, and ocular manifestations of myasthenia. Infants may require respiratory support and are treated with plasma exchange and neostigmine. This form of MG will resolve on its own and does not necessitate treatment. Once the antibodies have been cleared, there will be a resolution of symptoms [52].

Congenital Myasthenia Gravis (CMG)

CMG is a rare group of genetic conditions that are due to functionally abnormal proteins that affect neuromuscular transmission which results in fatigable weakness. The onset of symptoms varies and is commonly seen at birth, but may go unrecognized until adolescence or adulthood [53–55]. CMS is further classified based upon the location of the defect. Presynaptic defects account for approximately 7–8%, synaptic defects are estimated at 14–15%, and the remaining 75–80% are due to postsynaptic defects [53–57].

Males are more commonly affected than females with an estimated ratio of 2:1. Almost all CMS subtypes follow an autosomal recessive pattern except for the slow channel syndrome which is an autosomal dominant disease. The classification and diagnosis of this syndrome is based on clinical features, response to acetyl cholinesterase inhibitors (AChEi), and electrophysiological study findings. Incomplete ophthalmoparesis, ptosis, and mild facial paresis are often seen during infancy. Ophthalmoparesis and facial paresis progress during childhood and infancy along with generalized weakness and fatigue. Often these are associated with other features such as high arched palate, facial dysmorphism, arthrogryposis, and scoliosis. Episodic respiratory crises can occur with any form of CMS but is most commonly seen in patients with acetylcholinesterase deficiency [53, 58, 59].

Diagnosis

The diagnosis is based upon the clinical history and physical examination findings. There are few simple bedside tests such as ice packs and tensilon tests which help to make clinical decisions in an emergency situation. The diagnosis is confirmed by the presence of antibodies against proteins/receptors in neuromuscular junctions along with the electrodiagnostic studies such as repetitive nerve stimulus and single fiber EMG. Genetic studies are warranted only in patients with suspected CMS.

Morbidity

The most common cause of morbidity in patients is respiratory insufficiency due to a rapid and significant involvement of bulbar and respiratory muscles. Respiratory

compromise should be dealt with by suctioning secretions, noninvasive ventilation, or intubation. In 30–40% of cases, the cause of myasthenic crisis is idiopathic; however, a relationship between certain factors has been observed in the remainder of the cases. These factors include viral or bacterial infections, surgery, physical stress, changes in medication (initiating or stopping steroids, changes in acetylcholinesterase dosage), or initiation of drugs that interfere with neuromuscular transmission. Decubitus ulcers and DVT should also be prevented with appropriate measures in patients with decreased mobility. There is also a risk of several complications when treating with IVIG or PE [60, 61].

Treatment

Acute Management

Acute management involves observation in the pediatric intensive care unit (PICU) and provision of required supportive measures. Here, it is important to differentiate between myasthenic crisis and cholinergic crisis, as medication for myasthenic crisis will worsen the latter. Constant cardiorespiratory observation is vital, particularly because of the poor correlation between initial pulmonary function tests and the unstable nature of respiratory status in MG. Several studies have indicated that negative inspiratory volume (NIV) can be used to stave off requirements for intubation [62]. If NIV is begun before hypercapnia has set in, it can improve muscle fatigue and hence prevent total failure of the respiratory muscles. It is also useful when providing respiratory support to patients post extubation. Bi-level positive airway pressure (BiPAP), in particular, is especially useful and addresses the issue in a two-pronged manner. The positive inspiratory pressure it provides overcomes upper airway resistance, and the expiratory pressure helps prevent muscle fatigue and supports oxygen flow [63]. Patients with moderate to severe MG or myasthenic crisis can also be given short-term therapy with plasmapheresis or IVIG to clear the system of causal antibodies and induce rapid improvement. Recommendations for plasmapheresis are a total of five sessions on alternative days. IVIG is given over a 2–5 day period at a standard dose of 2 g/kg up to 150 g. Repeat IVIG treatments can be given every 4–8 weeks in patients who fail to improve or respond to other treatments [61].

Maintenance Therapy

Myasthenic maintenance therapy is considered as a non-neuromuscular emergency and should be managed in the outpatient setting (details beyond the scope of this textbook).

Prognosis

The prognosis for juvenile myasthenia gravis is much better than adult myasthenia gravis with more patients undergoing remission, both spontaneous and post-drug therapy. Remission rates are dependent on ethnicity as well as age (prepubertal children have the highest rates of spontaneous remission) [64]. Patients who undergo incomplete remission will often have a high quality of living and near normalcy when kept on drug therapy lifelong [47].

Botulism

Botulism is a presynaptic neuromuscular transmission failure caused by the botulinum toxin which is produced by an anaerobic, Gram-positive, spore-forming bacteria – *Clostridium botulinum*. It is commonly found in dirt, dust, and aquatic sediment. The bacteria produces six different subtypes of toxins labeled as A–G though only A, B, E, and F cause illness in humans [65]. It affects both infants and the adult population; however, it is more common in the pediatric age group with an estimated mortality rate of <5% [66]. In 2006, infant botulism was reported in 26 countries, with the United States having the largest incidence [67]. Every year 80–100 children are hospitalized in the United States because of infant botulism [68]. 15–30% of infantile botulism cases are linked to contaminated honey containing spores, while the rest is hypothesized to be due to swallowing of inhaled spores [69].

Pathophysiology

Botulinum toxin is absorbed across the intestinal mucosa and circulates through the bloodstream and lymphatics. In this way, it is carried to motor nerve terminals where it binds to its substrate presynaptic proteins called SNAREs (Soluble N-ethylmaleimide-sensitive factor-attachment protein receptors) [70] SNAREs are proteins present on both vesicles containing neurotransmitters as well as the presynaptic plasma membrane. Their role is to facilitate exocytosis and neurotransmitter release [71]. The botulinum toxin cleaves the SNAREs preventing neurotransmitter release, thus leading to blockage of transmission at cholinergic synapses.

Clinical Features

The clinical feature of botulism mimics myasthenia gravis. The symptoms usually start within 48 hours after ingestion with a prodrome of nausea, vomiting, constipation, and diarrhea. Affected child presents with descending paralysis usually started at eyes with ptosis, ophthalmoparesis, followed by facial weakness, dysarthria, and dysphagia. Progression leads to proximal limb weakness, areflexia, and respiratory failure. In infants, it is difficult to recognize, often presented with irritability, poor suck, and lethargy [13]. One of the important clinical features in patients with botulism has an involvement in the autonomic nervous system specifically affecting the parasympathetic nervous system resulting in dysautonomia. The symptoms include xerostomia, anhidrosis, mydriasis with nonreactive pupils, postural hypotension, and bowel and bladder hypomotility [72].

Diagnosis

If botulism is suspected, stool samples and serum should be taken immediately for further testing, but diagnosis is based on clinical history and physical examination findings along with supportive evidence of electrodiagnostic findings. The nerve conduction studies show decreased compound muscle action potential (CMAP) with normal latencies and conduction velocity. The repetitive nerve stimulus (RNS) shows typical features of presynaptic failure such as increase in amplitude (increment) with high frequency repetitive stimulus (up to 50 Hz) [73]. Needle EMG

findings vary and depends on timing of the study, but signs of denervation potentials like fibrillation and positive waves can be seen within a week [73]. As the disease progresses, they may not have CMAP or increment response to RNS due to progressive axonal loss. Recovery is slow over weeks to months and often incomplete; fatigue is one of the most common complaints during the recovery process [74].

Treatment

Treatment of botulism primarily centers on supportive care. Patients can be treated with botulism antitoxin as an adjunct to supportive measures in order to clear out unbound antibodies and hasten recovery. Treatment with antitoxin cannot reverse the effects of toxin that has already bound [75].

Supportive Care

Management primarily involves maintaining airway patency and ventilation. In case of respiratory dysfunction, elective intubation should be considered, as patients who are intubated after respiratory arrest are more likely to die than those who have been intubated electively [76]. Patients should also be monitored in the ICU for autonomic symptoms. Nutritional support is provided by feeds administered through a gastric tube. Constipation can be relieved with stool softeners [69].

Specific Treatment

Botulism antitoxin was approved in the United States by the Food and Drug Administration (FDA) and Center for disease control (CDC) in 2013. The antitoxin works by binding circulating unbound toxin, thus preventing progression of the disease and shortening the duration of illness and mechanical ventilation [77]. If ingestion of contaminated food was recent, gastric lavage may be attempted.

Prognosis

With adequate supportive care and in the absence of secondary complications like infection or hypoxia, patients will often begin recovering at 4 weeks [69, 70]. The duration of the recovery period is dependent on how long it takes to form new synaptic endings and motor end plates. A majority of the patients will show slow improvement over the course of 10 days to 2 months; however, some symptoms may take a year to resolve (especially in patients with dysautonomia symptoms). Patients will eventually have complete neurological recovery [70]. Case fatality rate is less than 1% in the United States [78]. Higher mortality rates are associated with larger doses of toxin ingested, a short incubation period, and botulism due to Toxin A versus Toxins B and C [70].

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Management of Pain in Neuromuscular Disorders

10

Vovanti T. Jones and William Christensen

Defining Pain

Pain is the most commonly cited reason that Americans access the health care system, and it is noted to be the leading cause of disability in the United States per the National Institute of Health (NIH) [1]. Chronic pain affects more than 75 million individuals in the United States and accounts for 20% of all outpatient visits [2]. Health economists have determined that the annual economic burden of chronic pain in the United States ranges from $560 to $635 billion yearly, which is greater than the total annual cost of cancer ($243 billion), heart disease ($309 billion), or diabetes ($188 billion) [5].

Pain has been formally defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [3]." Furthermore, pain is a universally subjective and multidimensional experience with foundations rooted in the biopsychosocial model [4]. As such, it is important to acknowledge that pain can be experienced by individuals in the absence of active and ongoing tissue damage (e.g., allodynia, fibromyalgia, phantom limb pain, somatic symptom disorder). This is due to an incomplete understanding of the intricate interplay of the central nervous system and the peripheral nervous system, in which a pain signal can persist despite termination of a painful stimulus. In this situation, pain becomes maladaptive and contradictory to the evolutionary imperative in which pain serves to mitigate damage by allowing an individual to safeguard themselves from the potential sources of harm. Indeed, acute pain traditionally serves to alert the individual that there is a form of noxious stimulus negatively impacting the

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body. For example, an individual will quickly withdraw their hand after touching a hot pan to avoid further tissue damage; alternatively, a person with intense abdominal pain on the verge of rupture of their appendix will respond by going to the emergency room.

Classification and Characterization of Pain

Pain may be characterized in a multitude of ways including time course, intensity, location, and etiology. With respect to duration, pain is arbitrarily but operationally defined as acute (pain lasting less than 3 months) or chronic (pain lasting greater than 3 months). Subacute pain is a recognized subset of acute pain and denotes that the pain has been present for more than 6 weeks, but less than 3 months [6]. Determining the duration of pain has implications with respect to both diagnostic and therapeutic management; an individual suffering from 3 days of acute lower back pain will be evaluated much differently from a patient who has had 8 months of chronic low back pain. Elucidating duration can be quite challenging to quantify in cases where pain onset is insidious (e.g., osteoarthritis).

Characterizing pain intensity can be achieved through several methods. One of the simplest approaches to characterize pain intensity in a patient is using the *Verbal Descriptor Scale*, which asks patients to describe their pain as mild, moderate, or severe. Another common methodology often utilized by physicians is the *Verbal Numeric Analog Scale*, which asks patients to rate their pain on a scale from 0 to 10, with zero being "no pain" and 10 being the "worst pain imaginable." Alternatively, the *Visual Analog Scale* asks patients to document their pain by making a mark on a vertically or horizontally drawn line with the words "no pain" on one end and "worst pain ever" on the opposite end. Artistic renditions of a pain scale are helpful for those who have difficulties in characterizing their pain into words, particularly in young children, non-native speakers, and the elderly (Fig. 10.1). For patients who are incapable of reporting their pain due to intubation, aphasia, or other impairment; common alternative pain rating tools include the *Critical Care Pain Observation Tool (CPOT)* and the *Behavioral Pain Scale (BPS)* [7]. Each of these approaches can be used to assess and monitor a patient's degree of pain over time. Temporal

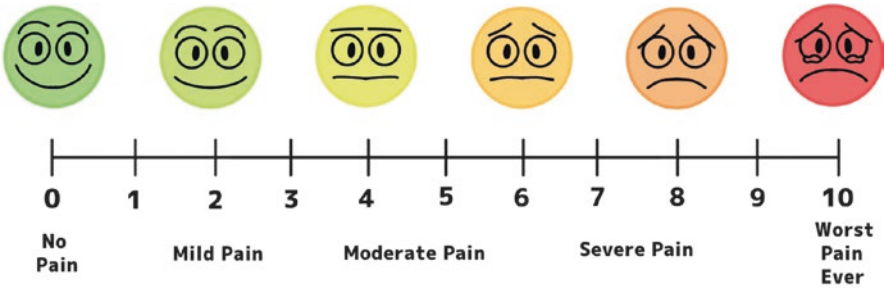

Fig. 10.1 Example of a Visual Analog Scale. (Illustrated by Caiden Christensen)

monitoring of the patient's pain permits the physician to determine if there is progression of the underlying disorder, can help to identify temporal patterns of the patient's pain, can help to characterize modifying (alleviating/aggravating) factors, and can serve to determine the impact of an intervention with respect to mitigation of the patient's pain.

Pain localization can be performed by various methods. The simplest method is simply asking the patient to state the location of their pain and/or to identify painful areas using their hands. Oftentimes, having the patient point to the area with a single finger can serve to help localize the pain generator. The *Ransford Pain Drawing* is another useful tool to allow patients to indicate where they perceive key symptoms on a diagram, utilizing various symbols (i.e., stabbing, burning, pins and needles, and numbness) [8].

Pain Pathophysiology

Elucidation of pain etiology requires a fundamental understanding of the different taxonomies of pain as well as a basic understanding of underlying pathophysiology. Peripheral pain receptors, known as *nociceptors*, serve to initiate transmission of noxious, potentially damaging stimuli to the central nervous system through nerve fibers. There are two types of nociceptors: high-threshold mechanoreceptors (HTM), which respond to mechanical deformation, and polymodal nociceptors, which respond to variety of tissue-damaging inputs (i.e., cytokines, bradykinin, histamine, prostaglandins, and hydrogen ions). There are two physiologically distinct high-threshold afferent nerve fiber types that are known to conduct painful stimuli: fast (5–30 m/s), myelinated *A-delta (Aδ)* fibers which transmits noxious mechanical, heat, noxious-cold stimuli and are slow (0.5–2 m/s); more diffuse, unmyelinated type *C fibers* which transmits noxious mechanical, heat, and chemical stimuli (Fig. 10.2) The two fiber types explain why you first feel a sharp pain which then develops into a more diffuse, dull pain over time; this is known as *double pain sensation* [9]. *A-beta (Aβ)* fibers are myelinated and respond to non-painful stimuli such as vibration and light touch.

Nociceptive stimuli travel via the afferent nerve fibers of the pseudounipolar neuron, entering the dorsal root ganglia (DRG) and subsequently traveling centrally to the dorsal horn of the spinal cord where it synapses with second-order neurons, primarily in the Rexed laminae I (marginal zone)/II (substantia gelatinosa). In addition, a collection of fibers travels caudally and rostrally one to two spinal levels in the *Lissauer's tract* before entering the dorsal horn of the spinal gray matter. Axons from the second-order neuron then decussate across the anterior white commissure of the spinal cord and ascend via the spinothalamic tract to the ventral posterolateral nuclei of the thalamus. Third-order neuron fibers navigate the internal capsule and the corona radiata to synapse within the somatosensory cortex [10]. Signals to the somatosensory cortex, somatotopically organized into a homunculus, bring the pain to the minds' consciousness and makes localizing this pain in the body possible (Fig. 10.2).

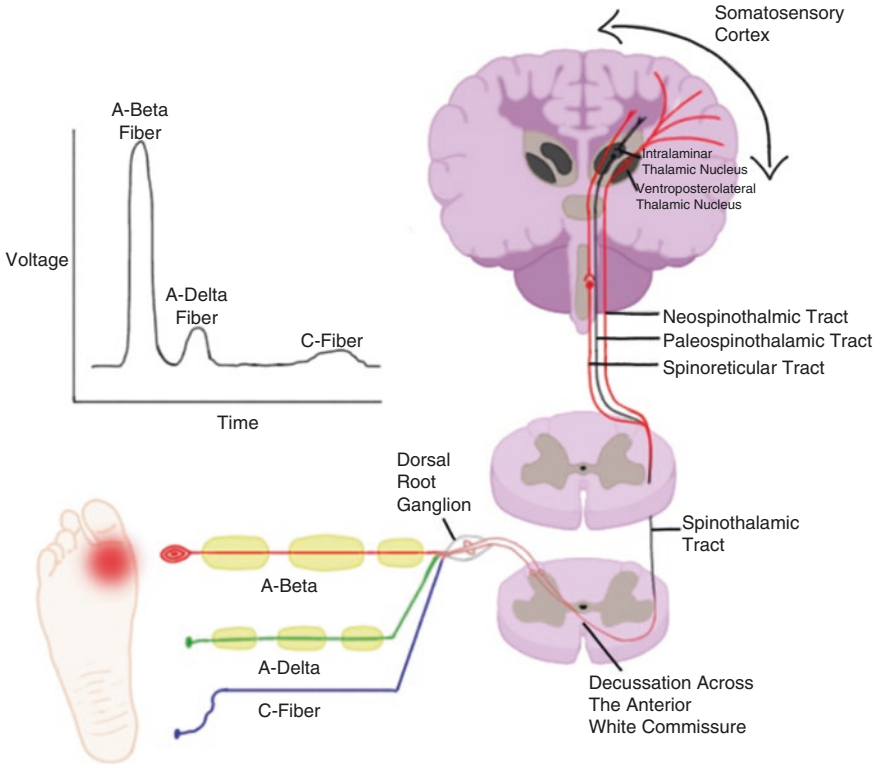

Fig. 10.2 Cerebral pain pathway and nociceptor fiber types. Aβ fibers are the largest in diameter and have the highest voltage output. Type C fibers are small unmyelinated fibers. Type Aδ are myelinated and are of intermediate diameter and voltage. (Illustrated by Caiden Christensen)

Somatic pain arises when noxious stimuli activate somatic nociceptors within the bones, muscles, joints, tendons, and ligaments; it tends to be easily localized due to the high density of nociceptors present in these tissues. *Visceral pain*, in contrast, arises from organ dysfunction and can result from inflammation, ischemia, and organ/capsular distension (e.g., cholecystitis, nephrolithiasis, appendicitis, small bowel obstruction, etc.); it tends to be poorly localized due to relative scarcity of nociceptors. With visceral nociception, the pain may occasionally be referred to somatic structures (e.g., myocardial infarction radiating to the arm) making localization even more difficult [11].

Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" and is often described as "burning," "tingling," or "shooting" in character. Neuropathic pain can be broadly classified as centrally-mediated, peripherally-mediated, or mixed [12]. *Centrally-mediated neuropathic pain* involves pain generated from lesions or disease within the spinal cord, brainstem, basal ganglia, and cortex. Common etiologies of centrally-mediated neuropathic pain include strokes, myelopathies, brain injuries, Parkinson disease, and

multiple sclerosis. *Peripherally-mediated neuropathic pain* involves peripheral sensitization initiated by damage to the components of the peripheral nervous system (PNS). Conditions that result in peripheral neuropathic pain include, but are not limited to, radiculopathy, plexopathy, entrapment neuropathy, diabetic neuropathy, phantom limb pain, trigeminal neuralgia, and Charcot-Marie-Tooth disease. Injury to the PNS triggers augmentation in the density of voltage-gated sodium ion channels within the nociceptors of the injured Aδ and C fibers and dorsal root ganglia as well as expression of additional ion channels (e.g., adrenergic receptors, calcium channels) [13]. These alterations may result in ectopic discharges and lowering of the depolarization threshold of nociceptors, resulting in symptoms consistent with neuropathic pain.

Protracted exposure to a noxious stimulus does not lead to adaptive dampening of the stimulus, but instead often leads to maladaptive sensory amplification, decreasing the pain threshold resulting in a state of *hyperalgesia*. This hyperalgesic state is thought to be secondary to nociceptors becoming hyperexcitable with a lower stimulus threshold. *Central sensitization*, also known as *secondary hyperalgesia*, results from hyperexcitability of neural pathways resulting in pain beyond the site of injury. Central sensitization requires noxious stimuli that is repetitive, intense, and unrelenting and has been shown to result in the upregulation of receptors [e.g., N-methyl-D-aspartate receptors (NMDAR)] and alterations of ion channels, thereby lowering of the depolarization threshold within the dorsal horn. Another contributing mechanism to development of neuropathic pain is *central disinhibition,* which occurs when CNS-based inhibitory pathways are downregulated in the dorsal horn; namely a reduction in inhibitory neurotransmitters and apoptosis of inhibitory interneurons driven by NMDAR-induced excitotoxicity [14]. *Allodynia,* in contrast, describes pain elicited from an innocuous stimulus that is *not* normally painful. For example, lightly stroking a cotton swab on the individual's skin elicits a subjective painful response. Touch-evoked pain is mediated by activation of non-nociceptive Aβ nerve fiber via mechanoreceptors eliciting a secondary hyperalgesia response within the central nervous system [15].

Pain in Neuromuscular Disorders

Neuromuscular disorders are a large group of disorders that affect different aspects of a motor unit. The site of damage could be the motor neuron (i.e., amyotrophic lateral sclerosis [ALS]), nerve (i.e., Charcot-Marie-Tooth [CMT]), neuromuscular junction (i.e., myasthenia gravis), peripheral nerve (i.e., acute inflammatory polyneuropathy [AIDP]/Guillain-Barre syndrome [GBS]), or the muscles (i.e., Duchenne muscular dystrophy) (Fig. 10.3). Neuromuscular diseases involved pathophysiology in the peripheral nerves or muscles as a part of the underlying disease process, which is distinctly different from pain generated by a general musculoskeletal disorder. Pain from neuromuscular disease is likely to be multifactorial through a variety of different mechanisms. Patients with neuropathic pain may develop secondary myofascial pain. In turn the myofascial pain may mimic the neuropathic pain;

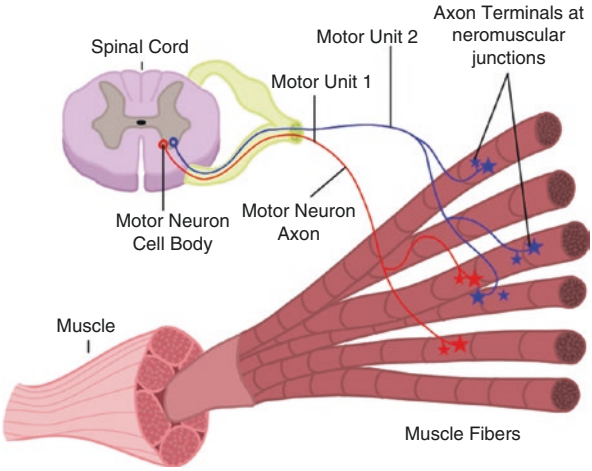

Fig. 10.3 Anatomy of a motor unit. From the anterior horn of the spinal cord, the axons of the alpha motor neuron synapse at the neuromuscular junction to directly control muscle fiber contraction. (Illustrated by Caiden Christensen)

however, the pain is coming from a distal location. This can be seen in patients with hereditary neuropathy. Skeletal muscle pathophysiology is likely to play a role in pain generation due to active muscle degeneration resulting from exercise-induced muscle injury and overwork weakness. Fatigue is also a component of pain and can be due to deconditioning and impaired muscle activity [16]. Therefore, it is very important to perform a detailed assessment of pain in those with neuromuscular disorders.

Evaluation of Pain in Persons with Neuromuscular Diseases

Taking a History

A detailed history helped the examiner identify and localize the source of the pain and can direct targeted therapy. The patient should be asked about the onset, timing and duration of their pain and about what provokes the pain. The patient should report the quality of the pain (i.e., burning, tingling, shooting). They should be asked about the location of the pain and whether that pain radiates to other parts of the body. The severity of the patient is often reported on a numerical scale (0–10), or in patients who are non-verbal a visual scale can be provided (Fig. 10.4).

The Pain Physical Exam

Upon first meeting a patient, early observation of the patient's mannerisms, interpersonal interactions, and gait can provide valuable information about the patient's current state of health. This information can provide a basis of comparison to the more structured portion of this exam. These less obvious to the

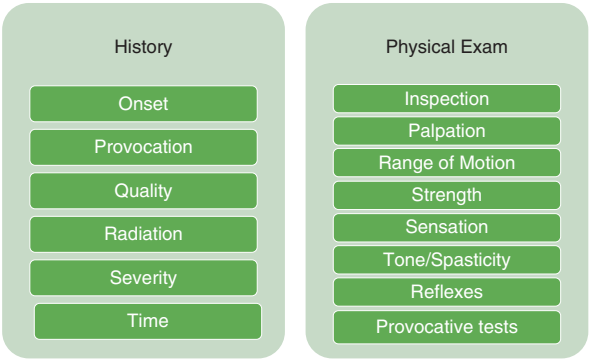

Fig. 10.4 The neuromuscular pain evaluation: history and physical components [16]

patient formal evaluations can help distinguish between inconsistent pain behaviors that may be displayed in some patients with reports of chronic pain (Fig. 10.3) [17].

1. *Vital signs*
   - Vital signs helped to determine the presence of systemic disease and assess for the patients' general health. Tachycardia and hypertension can be signs of uncontrolled pain responses but also may be signs of more severe systemic disease. Further medical evaluation can be considered in patients who present with abnormal vital signs.
2. *Mental status exam*
   - A brief mental status exam should be conducted in all patients with pain, as signs of mental deterioration should correlate with the patients' medical history and if not then further investigation into underlying pathology should be conducted.
3. *Inspection*
   - Head-to-toe inspection is an important part of the neuromuscular exam. Beginning at the affected area, the examiner should look for signs of trauma, rashes, edema, skin discolorations, and abnormal hair growth. Skin discoloration is commonly seen in patients with dermatomyositis. Abnormal hair growth can be seen in patients with peripheral neuropathy and peripheral vascular disease.
   - Evaluation of the large joints for deformities is also important. Shoulder subluxation can be a sign of deltoid/rotator cuff weakness in a patient with limb-girdle muscular dystrophy (LGMD), while scapular winging can be seen in patients with facioscapulohumeral dystrophy (FSHD) due to weak scapular stabilizing muscles.
   - Inspection of the spine focuses on evaluation of the normal curvature. In patients with neuromuscular diseases, spinal/postural evaluation can help identify the presence of neuromuscular scoliosis which can be a source of not only pain but can result in respiratory dysfunction. Early identification of scoliosis can lead to earlier interventions in patients who become

symptomatic. Hyperlordosis is often seen in patients with muscular dystrophy and can be a source of significant pain especially in ambulatory patients.
- Fasciculations can be seen at rest in patients most often with motor neuron disease (spinal muscular atrophy [SMA] and ALS) although they can occur in polyneuropathies, and in healthy people after exercise or with excessive stimulant intake. Myokymia can be seen in patients with neuromuscular disorders as well. Myokymis is involuntary worm-like repeated contractions seen under the skin that are often said to look like a "bag of worms" [17].

4. Palpation
   - Palpation is helpful to determine painful structures. Tenderness to palpation over specific structures can suggest that those areas are pain generators. For example, alteration in sensation producing allodynia or hyperesthesia could be associated with disorders like Charcot-Marie-Tooth (CMT) and Guillain-Barre syndrome (GBS). Palpation over a sensory nerve can indicate nerve entrapment (i.e., Tinel's).
   - Palpation over the spine and neck can help identify muscle spasms, myofascial trigger points, as well as further characterize spinal curvature.
5. Range of motion
   - Identifying functional limits is important to the evaluation and range of motion testing can assist with that. Range of motion should be tested both passively and actively. In patients with significant muscle weakness, active range of motion is typically first impaired compared to passive. In patients with prolonged impairment in movement, contractures can develop. Joint contractures can become painful and are difficult to stretch out. Plantar flexion contractures are often seen in patients with Duchenne's muscular dystrophy, while foot and hand/finger contractures can be seen in patients with CMT.
6. Strength
   - Evaluation of strength can help with identification of the etiology of weakness and pain. Patients with proximal greater than distal weakness could be suggestive of a myopathy such as that seen in patients with LGMD, while more distal weakness could be associated with Guillain-Barre syndrome. It is important to distinguish between true neurologic weakness and pain-induced weakness.
7. Muscle tone and spasticity
   - Alterations in muscle tone with or without spasticity can be a source of pain. In ALS, patients can have painful spasticity in their muscles which can place abnormally high forces on joints resulting in pain. Low tone can be seen in patients with spinal muscular atrophy and congenital myopathies.
8. Sensation
   - Sensory testing can help determine which part of the neural system is responsible for the patient's pain. Response to light touch, proprioception/vibration, and pain/temperature should be examined. Sensory deficits should be compared to dermatome charts and peripheral cutaneous nerve maps. Sensory alterations like allodynia can be found in many patients with neuropathic diseases, and it occurs in a non-dermatomal pattern. Sensory impairments in a dermatomal pattern could be consistent with disorders such as radiculopathy and mononeuropathies.

9. Reflexes
   - Deep tendon reflexes localize to specific levels of the spinal cord and can be helpful in determining the location of a painful lesion. Hypoactive reflexes can be seen in muscles with low tone or significant atrophy (i.e., myopathy). Clonus and Babinski sign can be seen in disorders of the anterior horn cell (ALS) and are indicative of an upper motor neuron disease in most cases.
10. *Gait*
    - As a part of the focused pain exam, the goal of the gait evaluation is to identify whether the gait is antalgic or if the functional pattern can result in abnormal forces across joints and/or abnormal positioning of structures. Identification of the gait pattern can give insight into the etiology of dysfunction and possible pain generator. In patients with proximal(gluteal) weakness, a waddling gait may be seen, while in patients with distal leg weakness (anterior tibialis), a foot slap or steppage gait pattern may be seen.
    - Equilibrium can also be tested in gait and stance. Impairments are suggestive of lesions in the sensory, vestibular, or proprioceptive systems. Equilibrium can be impaired in painful diseases such as GBS and diabetic neuropathy [16].

Pharmacologic Management of Pain

Non-opioid Pain Medications: Traditional First Line

Acetaminophen

- Inhibits prostaglandin synthesis in the CNS only
- Can be given parenterally as paracetamol
- Risk of hepatotoxicity with higher doses (<4 g/day recommended)
- Less systemic side effects than NSAIDs

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Inhibits prostaglandin and thromboxane synthesis by inhibiting the COX-1 and COX-2 enzymes that convert arachidonic acid into prostaglandins
- Can be administered orally, intravenously, rectally, topically, and rectally
- Risk of GI side effects. There are some NSAIDs that are more selective for COX-2 (meloxicam, celecoxib, and diclofenac), thereby reducing the risk of GI side effects

Non-opioid Pain Medications: Antidepressants

Tricyclic Antidepressants (TCAs)

- TCAs are considered first-line treatment
- Inhibit serotonergic and noradrenergic reuptake
- Have analgesic properties independent of their antidepressant and sleep effects

- This drug class includes: amitriptyline, nortriptyline, imipramine, doxepin, desipramine, and clomipramine. These drugs are relatively inexpensive and come in genetic form [18]
- Second-generation TCAs (nortriptyline and desipramine) are preferred over amitriptyline due to a lesser side effect profile [19]
- A potential severe side effect is the development of QT_C prolongation resulting in cardiac arrhythmias. Risk of overdose and death. Do not use in patients with cardiac dysrhythmia or prior myocardial infarctions. Caution in patients with Urethral outlet obstruction (i.e., BPH) or cognitive dysfunction
- Can take 6–8 weeks before full effects are seen

Selective Serotonin Reuptake Inhibitors (SSRIs)

- This drug class includes citalopram, fluoxetine, escitalopram, paroxetine
- Inhibits presynaptic reuptake of serotonin resulting in increased stimulation of the serotonergic pathway.
- Pain benefit may be due to reduction of depression which triggers/exacerbates pain production and coping
- There are fewer side effects versus TCAs
- Contraindicated in patients with narrow-angle glaucoma

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

- This drug class includes duloxetine, venlafaxine, desvenlafaxine
- Inhibits the presynaptic reuptake of serotonin and norepinephrine
- Duloxetine is FDA approved for diabetic peripheral neuropathy, fibromyalgia, generalized anxiety, and major depression.
- Costs more than TCAs typically
- Fewer side effects versus TCAs
- Venlafaxine has been associated with hypertension [20]

Non-opioid Pain Medications: Membrane-Stabilizing Agents/ Anticonvulsants

Gabapentin and Pregabalin®

- Bind to the α2δ subunit of L-type calcium channels to prevent increased trafficking of calcium due to nerve injury, thereby inhibiting pain signals
- Decreases glutamate, norepinephrine, and substance P
- Used for neuropathic pain found in diseases like diabetic neuropathy and Guillain-Barre syndrome
- Less severe side effects compared to TCAs
- Common side effects: edema (worse with gabapentin), sedation and dizziness
- First line to use in the elderly and others who cannot tolerate TCAs [21]

Carbamazepine (Tegretol®) and Oxcarbazepine (Tileptal®)

- Inhibits voltage-gated sodium channels

- FDA approved for trigeminal neuralgia
- Carbamazepine can have serious adverse effects: hyponatremia, hepatic injury, rash, aplastic anemia, and agranulocytosis. Blood levels must be monitored closely

Other agents such as valproate (Depakote®), topiramate (Topamax®), lamotrigine (Lamictal®), and tiagabine (Gabatril®) have shown some efficacy in the treatment of chronic pain.

Non-opioid Pain Medications: Topicals

Lidocaine (Gel, Cream, Patch, Viscous)

- Have antinociceptive effects
- Works by blocking voltage-gated sodium channels
- Poor systemic absorption allows for almost no systemic side effects
- Provides localized treatment with limited depth of penetration (i.e., for localized peripheral nerve pain and post-herpetic neuralgia)
- Dosing: Lidocaine patches/gel 5% (or over-the-counter 4%); apply up to 3 patches for 12 hours on and 12 hours off.
- The lidocaine patch 5% should be avoided in patients receiving Class I antiarrhythmic medications (i.e., mexiletine) and in patients with severe hepatic dysfunction [22].

Diclofenac Gel

- Good for pain with an inflammatory component
- Minimal systemic absorption, therefore less risk of bleeding and GI upset compared to oral NSAIDs

Capsaicin

- Binds $TRPV_1$ receptors causing nociceptive axon terminals to degenerate.
- Typical dosing is capsaicin 0.025% or 0.075% 3–4 times daily.
- Capsaicin can be applied as a patch or a cream [23].

Drug compounds

- Some pharmacies are able to compound multiple common pain-relieving medications into creams or gels for topical relief. Often medications like gabapentin and lidocaine are used.

Non-opioid Pain Medications: Muscle Relaxants

This group of medications has been found to be effective in patients with musculoskeletal pain. Side effects include sedation and anticholinergic effects. Typically, these are well tolerated [24].

- Methocarbamol (Robaxin®)
- Cyclobenzaprine (Flexeril®)
  - Acts primarily within the CNS at the level of the brainstem
  - Causes a reduction of tonic somatic motor activity of both δ- and α-motor neurons
  - Has been shown in randomized clinical trials to be effective in patients with fibromyalgia [25].
- Carisoprodol (Soma®)
- Metaxalone (Skelaxin®)

Opioid Pain Management

Opioids are the most common medication class used for severe pain. Opioids bind to the mu, kappa, and delta receptors in the CNS and in peripheral tissues (Table 10.1). They reduce neurotransmitter signaling by reducing the influx of calcium into the presynaptic terminal resulting in reduction of the amount of neurotransmitter that can be released. Hyperpolarization of the postsynaptic neuron is caused by the opioid induced increased in the influx of potassium.

Although opioids have been shown to be effective in treating neuropathic pain, they are considered to be second-line treatments in part due to their side effect profile. The side effects and risks associated with both acute and chronic opioid use can be significant [22]. Opioids that bind Mu_2 receptors can cause respiratory depression, sedation, vomiting, pruritus, anorexia, and physical dependence. Mu_1 receptor binding results in analgesia, while Delta receptor binding can cause both peripheral and spinal analgesia. Opioids that bind Kappa receptors can cause sedation, respiratory depression, euphoria, dyspnea, analgesia, and psychomimetic effects. Constipation is a very common side effect due to opioid's actions on the enteric

Table 10.1 Common opioid analgesics and receptor selectivity

Common opioid analgesics	Receptors selectivity
Morphine	Mu, Kappa, Delta
Codeine	Mu, Delta
Hydrocodone	Mu, Kappa
Oxycodone	Mu, Kappa
Methadone	Mu, Delta, Kappa Also acts as a NE and serotonin reuptake inhibitor and NMDA antagonist
Fentanyl	Mu, Kappa
Meperidine	Mu
Hydromorphone	Mu
Tramadol	Weak Mu Also acts as a weak NE/serotonin reuptake inhibitor

Opioids bind to the Mu, Kappa, and Delta receptors with varying affinities resulting in their differing patterns of pain relief. Mu receptors bind to all opioids, while Kappa and Delta receptors' binding capacity vary among the opioids [25]

nervous causing sustained contractions of the smooth muscles of the gut which result in reduced motility. In chronic use, sexual dysfunction can occur due to opioid-induced hypogonadism [25]. The results of recent studies have found that opioid misuse and the development of addiction vary from 5% to 50%; therefore, careful consideration of the patient must be made before prescribing this class of medications [22]. Drug overdoses are treated with naloxone and longer acting opioids like methadone are used to help wean people off of them.

Tramadol is a weak mu opioid. Several studies have shown that tramadol inhibits serotonin and norepinephrine, which synergistically enhances the opioid mechanism of action. Tramadol can be effective in opioid-resistant chronic pain states and other painful conditions. It has less severe side effects compared to traditional opioids. Naloxone does not revere all the antinociceptive or analgesic effects of tramadol [26].

Management of Neuropathic Pain

Neuropathic pain is caused by a direct injury or disease of the peripheral nervous system. It can be caused by many different diseases including diabetes mellitus, herpes zoster, chemotherapy, and traumatic injuries such as a brachial plexus avulsion [27]. Neuropathic pain is also a symptom of neuromuscular disorders including hereditary sensorimotor neuropathies (HSMNs) and acute and chronic inflammatory demyelinating polyneuropathies (AIDP & CIPD). Neuropathic pain is often described as "burning," "tingling," or "shooting" in character. Persistent neuropathic pain can impair function as well as contribute to declining emotional health ultimately causing a decline in health-related quality of life [27].

Treatment of neuropathic pain medication can be difficult, and studies have shown that patients with neuropathic pain often report less satisfactory pain relief. The evidence of neuropathic pain treatments is continuing to evolve. There have been several randomized controlled trials (RCTs) on different medications for

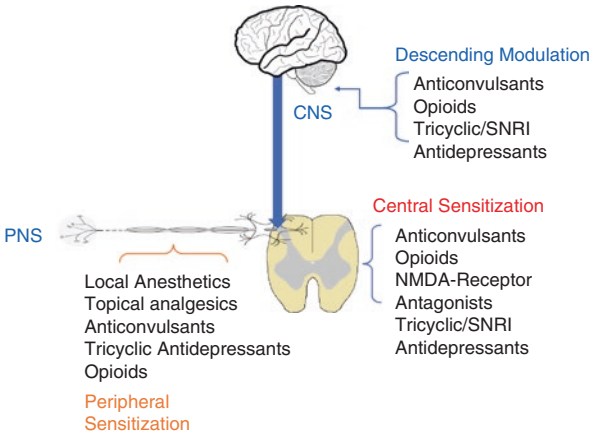

Fig. 10.5 Mechanism of action of typical pharmacologic agents for neuropathic pain. Treatments affect the central nervous system and/or are peripherally acting [18–22]

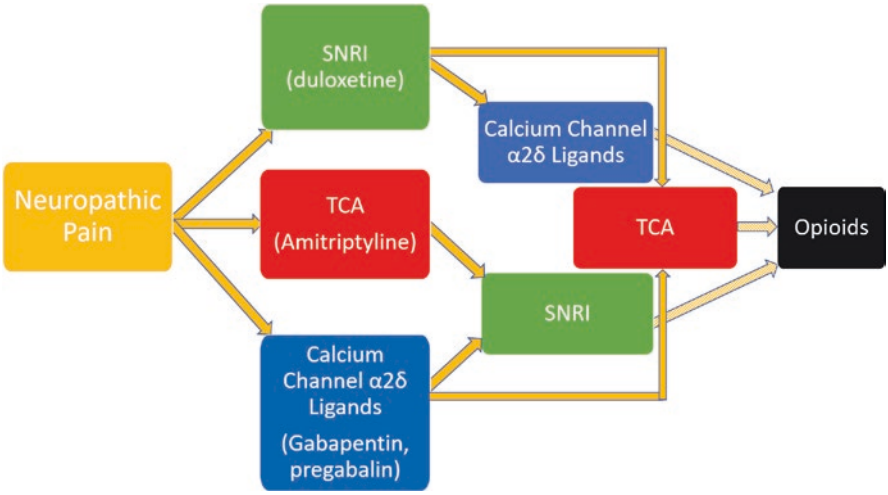

Fig. 10.6 Neuropathic pain treatment algorithm. First line – SNRI, TCA, calcium channel αδ2 ligand [27, 55]

different types of neuropathic pain disorders [28] (Fig. 10.5). The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) published guidelines for pharmacologic treatment of neuropathic pain in 2015 (Fig. 10.6).

First-Line Therapeutic Treatment (Fig. 10.6)

- *Tricyclic antidepressants:* Amitriptyline, imipramine, nortriptyline, desipramine, clomipramine
- *Serotonin-norepinephrine reuptake inhibitors (SNRIs):* In particularly duloxetine
- *Gabapentin and pregabalin:* Considered the best-established treatment of peripheral neuropathic pain. Effectiveness is increased when combined with TCAs or opioids in some reported cases [27] (Table 10.2)

Second-Line Therapeutic Treatment

- Topical agents: Lidocaine (gel or patches), capsaicin (cream or patches). The single application of an 8% capsaicin patch showed efficacy for up to 3 months in diabetic and nondiabetic painful neuropathies. The treatment can be repeated; however, the long-term effects on epidermal nerve fibers have not been elucidated [29].
- Tramadol: Second line due to the potential risk of abuse. Used with caution in patients on antidepressants.

Table 10.2 First-line pharmacologic treatments of neuropathic pain [25, 55]

Drug class	Medication	Dosing	Common side effects	Other
Selective serotonin and norepinephrine reuptake inhibitors	Duloxetine	20-–30 mg QHS Max 60-120 mg per day	Headache Dry mouth Nausea	In higher doses, can treat depression Dose adjusted for renal or hepatic impairment
	Venlafaxine	37.5 mg QHS Max 225 mg		Risk for serotonin syndrome when in conjunction with TCAs Trial 4–6 weeks
Calcium channel α2δ ligands	Gabapentin	100 mg QHS or BID Max 3600 mg per day	Sedation/lethargy Peripheral edema	Dose adjusted for renal dysfunction Dose taper for stopping recommended Trial 4–8 weeks
	Pregabalin		Same as gabapentin	
Tricyclic antidepressants	Amitriptyline	20-25 mg QHS Max 75-150 mg daily	Weight gain Anticholinergic effects-dry mouth, dry eyes, urinary retention	Caution in the elderly- more sensitive to the anticholinergic effects
	Nortriptyline	10-25 mg QHS Max 75-150 mg daily	May cause/worsen cognitive impairment	Trial 6–8 weeks
	Imipramine	10-25 mg QHS Max 75-100 mg daily		
	Desipramine	10-25 mg QHS Max 75-100 mg daily		

These Drugs Have Had Inconsistent or Negative Results in Clinical Trials

- Antiepileptics other than α2δ ligand binders (i.e., topiramate, levetiracetam, valproate) have reported negative or inconsistent results. Some may be effective in certain populations.
- Oromucosal cannabinoids have variable effectiveness.
- Selective serotonin reuptake inhibitors (SSRIs)
- NMDA antagonists.
- Mexiletine.
- Topical clonidine [27].

Nonpharmacologic Management

- TENS unit.
- Spinal cord stimulation may have some efficacy by altering the dorsal horn processing and transmission in the tract of Lissauer and suppression of sympathetic outflow from the intermediolateral gray column of the spinal cord [30].

Novel Treatments in Development for Neuropathic Pain

Pharmaceutical companies and researchers continue to investigate novel approaches to neuropathic pain treatment. EM 401-003 is a novel angiotensin type II antagonist that is effective in a phase II clinical trial in postherpetic neuralgia. Nav1.7 antagonists are selective sodium blocking agents that are being researched for effectiveness [31].

Neuroablative procedures are typically not warranted due to the high probability of long-term worsening in pain. Ablation can cause temporary relief but patients may develop sensory or motor deficits. Ablation of sympathetic fibers, visceral plexi, and medial branch nerve blocks for spine facet joints has shown some efficacy.

Spasticity Management

Spasticity is a motor disorder characterized by a *velocity-dependent* increase in the tonic stretch reflexes (muscle tone) with exaggerated phasic stretch reflexes (tendon jerks, clonus) resulting from hyperexcitability of the stretch reflex. Spasticity is not only seen in patients with neuromuscular disorders like ALS and PLS, but it is also seen in other conditions such as stroke, multiple sclerosis, cerebral palsy, spinal cord injury, and traumatic brain injury. Spasticity is a part of the upper motor neuron syndrome (UMNS), which refers to motor behaviors that occur due to a lesion above the level of the alpha motor neuron resulting in the loss of descending inhibition and hypersensitivity of the reflex arc in the spinal cord [32]. The Modified Ashworth Scale, Visual Analog Scale, Spasm Frequency Score, and Tardieu Scales are clinical scales that can be used to assess spasticity.

Pain is a functionally limiting negative symptom of spasticity. This pain can be secondary to the abnormal posturing, the development of contractures, and/or the increased risk of decubitus ulcer development due to decreased ability of people to properly position themselves to relieve pressure when sitting or lying down. Strong spasms can result in bone fractures and joint subluxation/dislocation which can result in musculoskeletal pain.

Spasticity may have some functional benefits in patients (i.e., helping with ambulation and providing stability in sitting/standing); therefore, these benefits have to be considered before spasticity-specific pain relief is initiated. Conservative management includes stretching, vibration, biofeedback, heat, cold, splinting, and serial casting. In patients with neuromuscular diseases, splinting and serial casting are less commonly used compared to other spasticity causing conditions.

Pharmacological Treatments of Spasticity

There are four oral medications FDA approved for spasticity due to a CNS disorder: baclofen, tizanidine, dantrolene, and diazepam [32, 33].

- Baclofen
  - Mechanism: $GABA_B$-selective agonist that inhibits the release of excitatory neurotransmitters and simultaneously reduces postsynaptic membrane depolarization to inhibit neuronal transmission. There is also evidence that it may reduce substance B in the spinal cord.
  - Dosing: 5–80 mg/day (FDA approved). Higher doses have been used in some cases.
  - Side effects: Sedation, lowers seizure threshold, cognitive impairment, weakness, and GI symptoms.
  - Sudden withdrawal is associated with seizures, hallucinations, and rebound spasticity.
- Diazepam (benzodiazepines)
  - Facilitates postsynaptic effects of GABA on $GABA_A$ receptors causing enhanced presynaptic inhibition.
  - Effective for painful spasms
  - Side effects: Sedation, memory impairments, CNS depression, and weakness. There is also the potential for dependency and abuse.
  - Dosing: Diazepam 2–5 mg BID initially to max 60 mg/day.
  - Clonazepam has also been used in some cases.
- Clonidine
  - Mechanism: Acts as an Alpha-2 agonist and provides presynaptic inhibition.
  - Can be used as a transdermal patch or orally.
  - Side effects: Hypotension, cognitive impairment, fatigue.
  - Sudden withdrawal can result in severe reflex hypertension.
  - Dosing: 0.1–0.3 mg patch weekly or 0.1–0.4 mg/ divided per day.
- Tizanidine
  - Mechanism: Acts as a central and spinal-acting alpha-2 adrenergic agonist. Enhances presynaptic inhibitory modulation of spinal reflexes.
  - Side effects: Sedation, dizziness, dry mouth, possible liver damage (monitor LFTs), hallucinations, bradycardia.
  - Dosing: 2–4 mg/day. Max 36 mg/day.
- Dantrolene sodium
  - Mechanism: Works directly on muscle to prevent calcium release from the sarcoplasmic reticulum to inhibit muscle contraction.
  - Indicated primarily in cerebral forms of spasticity.
  - Side effects: Weakness, liver toxicity (monitor LFTs), least likely to cause sedation.
  - Dosing: Initial 25 mg TID to max 400 mg/day total.
- Other less commonly used agents.
  - Cyproheptadine: Antihistamine, anti-serotonergic, and mild anticholinergic activity. Blocks postsynaptic denervated supersensitive spinal receptors.

- Cannabinoids: Etiology unclear but has seen success in patients with SCIs.
- Gabapentin/pregabalin

Local Treatments of Spasticity

In patients with some neuromuscular disorders (i.e., ALS, Lambert-Eaton myasthenic syndrome, and myasthenia gravis), large area local treatments of spasticity with intramuscular injectable medications are typically avoided. Patients with neuromuscular disorders are at increased risk for severe reactions to normally therapeutic dosing. These reactions include severe weakness, respiratory depression, dysphagia, and even death. Botulinum toxin to the salivary glands has been used for managment of excessive salivation in patients with bulbar symptoms related to ALS. In a study of patients with hereditary spastic paraparesis, botulinum toxin was effective in improving gait velocity and lower leg positioning [34].

In people without neuromuscular disorders who have localized areas of spasticity or have significant side effects from oral medications, chemoneurolysis and chemodenervation are two ways to block the nerve supply or muscle activity from weeks to years. These agents can be used in conjunction with oral agents and other modalities. These agents can help facilitate therapy and function while also reducing pain. Chemoneurolysis is performed with phenol or ethyl alcohol. These agents cause axonal necrosis and protein denaturation resulting in axonal destruction and demyelination. Patients can experience dysesthesias, muscle pain, weakness, or swelling. Phenol is associated with convulsions, CNS depression, and cardiovascular collapse if injected intravascularly. Chemodenervation is performed with botulinum toxin. Botulinum toxin blocks the presynaptic release of acetylcholine (ACh) at the neuromuscular junction. Botox® (onabotulinumtoxin A) and Xeomin® (incobotulinumtoxin A) are two FDA-approved medications for the treatment of spasticity [32].

Intrathecal Baclofen Pump (ITB)

An intrathecal baclofen pump allows the direct deposition of baclofen into the intrathecal space. This allows for reduced oral medications requirements and therefore reduced side effects. All other treatment options should be explored before consideration of an intrathecal pump. Referral to a physiatrist is advised. There are several risks associated with pump malfunctions including both withdrawal and overdose. Patient selection is very important [35]. There has been some success in people with Stiff-person syndrome [36]. In a study of two patients with ALS treatment with intrathecal baclofen, they found that ITB as a form of palliative treatment benefited patients even at the terminal phase of the disease by relief of painful spasms, making immobility more tolerable [37].

Surgical Interventions

Surgical interventions are less commonly seen in patients with neuromuscular disorders like ALS and muscular dystrophy but can be seen in disorders such as cerebral palsy. Orthopedic procedures such as tendon lengthening procedures or tendon transfer procedures (split anterior tibial tendon transfer) can be considered when plantar flexion contractures interfere with ambulation. This is more commonly seen in the pediatric population. Neurosurgical procedures such as rhizotomy and neuroablative procedures are rarely performed due to significant risk related to weakness post procedure. In a study of selective dorsal rhizotomy for four patients with hereditary spastic paraparesis, there was a significant reduction in muscular spasms and improvement in standing and walking stability without significant major side effects [38].

Other Pain Management Alternatives

Corticosteroid injections have not been found to work well with neuropathic pain; however, systemic corticosteroids can be beneficial in patients with an inflammatory component to their neuromuscular disorder, including the inflammatory myopathies polymyositis and dermatomyositis. Corticosteroids are not typically used for isolated pain chronically due to its effect on the adreno-pituitary axis and risks of steroid induced myopathy [39].

Alternatively, injecting local anesthetics have been shown to have little efficacy for long-term use due to their short duration of actions. In patients with pain that is non-responsive to oral therapy or patients who have significant side effects with oral therapies, intrathecal pain pump placement can be considered. Some medications used include within these intrathecal pumps are opioids, lidocaine, and other local anesthetics, baclofen, and clonidine [40]. The insertion of an intrathecal pump is a long-term decision and requires frequent follow-up with a physician for refills and pump management. Patients who receive these pumps must be very compliant and educated on the risks related with pump malfunction.

Transcutaneous electrical nerve stimulation (TENS) can help with pain control in patients with neuropathic pain. The use of the TENS unit is based upon the gate-control theory of pain. Gate-control theory proposed by Melzak and Wall in 1965 suggests that lamina II inhibitory interneurons can be activated directly or indirectly by stimulation of non-noxious large sensory afferents from the skin (Aβ fibers) that then suppress transmission in type C fibers, blocking the transmission of pain [41].

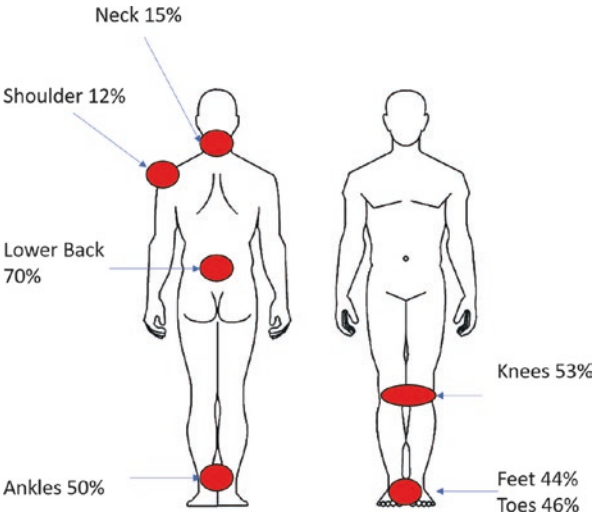

Fig. 10.7 Most common locations of pain in patients with CMT [42]

Neuromuscular Pain: Disease-Specific Treatments

Charcot-Marie-Tooth (CMT) Disease

CMT is the most common hereditary neuromuscular disease worldwide. In the United States, the estimated prevalence is of ~26,000. CMT type I is the demyelinating form and CMT type II is the neuronal form. Patients with CMT present with diffuse muscle weakness and distal atrophy of most commonly the intrinsic muscles of the feet and the peroneal muscles. The sensory deficits are typically less severe than the motor deficits [42].

Neuropathic pain is common among people with CMT. Pain is most often reported as cramps, paresthesia, and aching in the legs, associated with peroneal muscle atrophy. Pain is reported more frequently in the demyelinating forms like CMT A1. CMT A1 is associated with damage in Aδ type nerve fiber. Studies have shown 62–71% of people with CMT reported having pain, while 39% of patients reported pain that interfered with ADLs. The most reported sites of severe pain are: low back (70%), knees (53%), ankles (50%), toes (46%), feet (44%), neck (15%), shoulders (12%), hands (7%), and "other" (16%) (Fig. 10.7) [42].

Although patients with CMT report symptoms consistent with neuropathic pain; nerve damage is typically not the only source of painful stimuli. People with CMT have significant muscular weakness resulting in foot, ankle, and joint instability ultimately resulting in joint deformities. This alteration in normal biomechanics places higher stress on the entire musculoskeletal system resulting in pain. Prolonged immobility due to weakness and pain can create a general deconditioned state which has been associated with reduced pain tolerance [43].

Treatment of CMT-related pain is typically multifactorial. Neuropathic pain medications may be beneficial in addressing the pain associated with the direct

nerve damage, while adjuvant medications may be needed for the concomitant musculoskeletal pain. Neuropathic pain treatment options include: gabapentin, lyrica, TCAs, and serotonin and norepinephrine uptake inhibitors (SNRIs). These medications have limited efficacy and are often limited due to side-effects [43]. Resistance and insensitivity to opiates for neuropathic pain is common. Nonsteroidal anti-inflammatory drugs do not.

MSK pain treatment options include: NSAIDs, acetaminophen, and aspirin. Narcotic pain medications can be used including: oxycodone, hydrocodone, or codeine. Benzodiazepines can be used short term for muscle spasms.

Myotonic Muscular Dystrophy

Myotonic muscular dystrophy is the most common form of the dystrophic myopathies. Myotonic muscular dystrophy type I (DM 1) is caused by a polynuclear tight (CTG) triplet repeat on chromosome 19. Patients with myotonic muscular dystrophy have the involvement of almost all organ systems, most specifically the skeletal, cardiac, and smooth muscles. There are also major effects on the nervous, respiratory, and GI systems [44]. Studies have shown that as many as 70% of patients with DM 1 report pain. Pain in the leg, foot, hip, and knee contributed independently to the prediction of pain interference with physical function [45]. It is unclear whether the pain reported in this disorder is related to only the musculoskeletal components or does it also generate from the multiorgan system dysfunction because of activation of alternative pain pathways.

Myotonic dystrophy type 2 (DM2) is a dominantly inherited disorder affecting the chromosome 3q21.3. It presents with muscular weakness, myotonia, pain, and early cataracts. The lifetime prevalence of pain is 76%. Recent studies have shown that the mechanical hyperalgesia in DM2 compared to health controls is mainly present in the rectus femoris, trapezius, and thenar muscles, suggestive of a peripheral mechanism of pain in these patients. Weakness and pain are most commonly found in the proximal muscles, which suggest that the most affected muscles are also the most painful ones [46].

NSAIDs, carbamazepine, phenytoin, and a short course of corticosteroids have been used with success in some patients. Medications to alter muscle tone like baclofen and tizanidine have also been used in some patients [46].

Stiff-Person Syndrome

Stiff-person syndrome (SPS) is a disorder which causes progressive and fluctuating rigid and painful spasms that lead to muscle rigidity, spasticity, and difficulty with movement [47]. The incidence is approximately one in a million. Patients usually have normal sensation and motor function as well as normal cognition. The only neurological symptom typically present is muscular rigidity. The hallmark of this SPS is muscular rigidity, muscle spasms, and psychological symptoms (i.e., specific

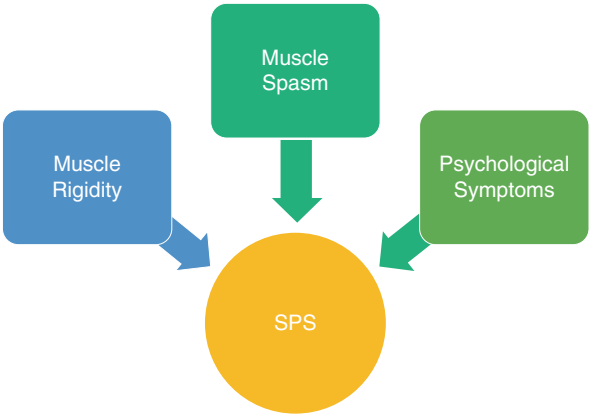

Fig. 10.8 Hallmark features of Stiff-person syndrome [47, 48]

phobias, generalized anxiety disorder, and depression) (Fig. 10.8). Commonly patients with SPS have stiffness starting in the trunk and progressing to the abdomen and lumbar region, resulting in stiffness of the lumbar spine. This stiffness can progress to other muscles of the body including the thorax causing difficulties with respiration. Facial muscles can also become involved resulting in limited facial movement and expression. Painful spasms can be triggered by auditory and tactile stimulation, and with severe spasms joint dislocations have been reported. A rare paraneoplastic variant of SPS occurs in 5% of cases and is associated with stiffness localized to the arms and legs [48].

The exact pathophysiology remains unclear; however, recent studies indicate the involvement of anti-GAD antibodies. 60–80% of patients with SPS have anti-GAD antibodies (Abs). GAD is an enzyme responsible for GABA synthesis in the brain and spinal cord. In patients with Stiff-person syndrome (SPS), examination of the nervous system shows that there is no structural damage to the GABAergic neurons. It is presumed that the impaired signals are secondary to pharmacological blockade from anti-GAD autoantibodies. The presence of anti-GAD autoantibodies is almost a pathognomonic finding in suspected cases of SPS. Newly identified antibodies to GABARAP, GlyRα1, and amphiphysin antibodies have all been found to inhibit GABA receptors resulting in SPS variants. Anti-amphiphysin Abs have been associated with paraneoplastic syndrome. Antibody titers do not correlate with the severity of the disease. Nerve conduction studies are normal; however, electromyography shows sustained muscle contractions and spontaneous discharge of normal appearing motor unit action potentials (MUAPs) [47].

Pain is the common feature of SPS due to the spasticity and rigidity. Treatments have been aimed at relieving these changes in muscle tone. Treatments include corticosteroids, benzodiazepines, plasmapheresis, intravenous immunoglobulin (IVIG), and various antibodies [47].

Corticosteroids are often used alone or in combination with other medications. Clinical trials have been inconsistent in showing major efficacy in patients with

SPS. Patients with classical symptoms of SPS typically respond well; however, sudden withdrawal can lead to autonomic dysfunction which could result in death [49].

Benzodiazepines are first-line treatment for patients with SPS due to their effects on the GABAergic nervous system as $GABA_A$ agonist. Diazepam: clonazepam can be used with gradually increasing doses over time. Typically, a divided dose of 5–100 mg of diazepam or 1–6 mg of clonazepam can be given initially. If patients are not responsive to these doses, caution has to be taken secondary to the side effect of respiratory depression and alterations of cognition/mental status and sedation that can occur with these medications [47]. Special attention must be paid to other medications that the patient may be taking due to the overlapping effects of sedation and respiratory suppression with medications like opioids.

Due to the role of the GABAergic system in Stiff-person syndrome, it is not surprising that other medications that have effects on the GABA system have been considered. Gabapentin, valproate, and levetiracetam have been shown in some studies to reduce the symptoms [49].

Baclofen is also considered a first-line treatment due to its agonistic effect on the $GABA_B$ receptors. It is often used to manage spasticity in patients after a stroke or brain injury. Oral doses of baclofen typically have to be titrated up to higher doses to get good effect in patients with SPS; therefore, the alternative to these higher doses include intrathecal baclofen. Intrathecal baclofen at doses between 50 and 800 mcg/day have been shown to cause significant relief of symptoms and patients with SPS [36]. Baclofen is not without its own risk and side effects. Often with oral baclofen, sedation is a limiting factor on dosages. Intrathecal baclofen requires internal placement of a pump and catheter directly into the spinal cord. There is significant risk of overdose and withdrawals that can be life-threatening due to autonomic dysfunction. A neurosurgeon is required for pump placement. Baclofen pumps require regular follow-up to check the function of the pump and the attached catheter. Typically, intrathecal pumps are managed by physiatry, neurology, or neurosurgery.

Plasmapheresis and intravenous immunoglobulin (IVIG) have been shown to be reasonable second-line treatment for Stiff-person syndromes in patients who have significant disability from their muscle stiffness. Plasmapheresis works to remove the anti-GAD autoantibodies, thereby reducing their blockade of GABA. One study showed that 56% of patients treated with plasmapheresis after failure of first-line treatment had some symptom relief. IVIG has been found to cause a decrease in anti-GAD autoantibodies resulting in decreased stiffness. IVIG may be considered after plasmapheresis due to the higher chance of adverse reactions with administration, especially in patients who have IgA deficiency [50].

Alternative therapy options are being researched including the use of rituximab administered via weekly infusions. A recent study showed that a patient treated with rituximab showed improvements in gait and ambulation. Cognitive behavioral therapy (CBT) to treat the psychological components of SPS has been beneficial to reduce the anxiety associated with increased muscle stiffness. CBT is often used in conjunction with medications [47]. Rehabilitation is also an important component in the treatment of the hyperlordosis related to axial muscle spasms, gait and

mobility impairments, muscle stiffness, and low back pain that can be seen in this disorder [48]. In a single case report, osteopathic manipulative treatment (OMT) is used as an adjunct to pharmacology to reduce somatic dysfunction and to reduce the frequency of exacerbations, thereby alleviating some of the painful symptoms [51].

Acquired Peripheral Nerve Hyperexcitability Syndromes (APNH)

Acquired peripheral nerve hyperexcitability syndromes are a group of disorders that lead to sustained muscle contractions and pain. Within this group of disorders is Isaacs' syndrome and Cramps-fasciculation syndrome.

Cramps-Fasciculation Syndrome

Fasciculations are brief asynchronous stretches of muscle fibers creating a visible contraction within the muscle. They are the result of involuntary activation of the motor units. The muscle contractions created by the fasciculations typically do not cause large joint movements, but they can sometimes cause movement at smaller joints. In healthy people, fasciculations can be normal and seen after intense exercise or even with consumption of caffeine or other neurostimulants. They are often seen in neuromuscular disorders like SMA, ALS, and Cramps-fasciculation syndrome.

Muscle cramps are painful involuntary contractions of all or some of a muscle. They can last a few seconds to a few minutes. EMG shows high frequency irregular bursts of motor unit action potentials (MUAPs). Muscle cramps can be seen in healthy individuals as well as in people with neuromuscular diseases. They are commonly seen in patients with neurogenic disorders (i.e., ALS) and metabolic myopathies (i.e., McArdle's disease). Cramps can improve with stretching in some cases. Contraction of a shortened muscle can trigger a cramp.

Patients with Cramp-fasciculation syndrome mostly present with post-exercise cramps and fasciculations which cause pain. Treatments with carbamazepine or phenytoin have been found to be effective in milder cases. Patients who are severely affected can be treated with plasmapheresis and immunosuppressive therapy [52].

Isaacs' Syndrome

Isaacs' syndrome (acquired neuromyotonia) is a disorder of the nerve potassium channels. Antibodies formed against the voltage-gated potassium channels suppress the outward flow of potassium. This results in hyperexcitability of the peripheral nerve leading to increased output to the muscles causing sustained contractions [53]. Isaacs' syndrome can occur alone or associated with other autoimmune diseases. It is characterized by the insidious onset of continuous muscle twitching. On EMG/NCS, myokymic (5–150 Hz) and neuromyotonia (150–300 Hz) discharges can be seen [44]. In some cases, fasciculation and fibrillations are seen. Nerve conduction itself is usually normal [53].

Phenytoin and carbamazepine have been found to be efficacious to the treatment of Isaacs' syndrome. It is thought that these antiepileptic drugs can reduce the function of the voltage-gated potassium channels. Patient was also released from plasma

exchange. A case report of a 70-year-old female with Isaacs' syndrome showed improvement in her symptoms with immunoadsorption treatment consisting of six plasmapheresis sessions over 17 days. The patient had a reduction in time for release of her sustained grip along with the reduction in muscle cramps (severity and duration) and pain related to these cramps [54].

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Correction to: Neuromuscular Urgencies and Emergencies

Niraj Arora, Raghav Govindarajan, Saurabh Kataria, and Premkumar Nattanmai Chandrasekaran

Correction to: N. Arora et al. (eds.), ***Neuromuscular Urgencies and Emergencies*****, https://doi.org/10.1007/978-3-030-53145-4**

The author's name was incorrectly placed as 'Sara Pretty Idiculla' and this has now been corrected to 'Pretty Sara Idiculla' in Front matter and chapters 4 and 5.

The updated versions of the chapters can be found at
https://doi.org/10.1007/978-3-030-53145-4_4
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Appendix

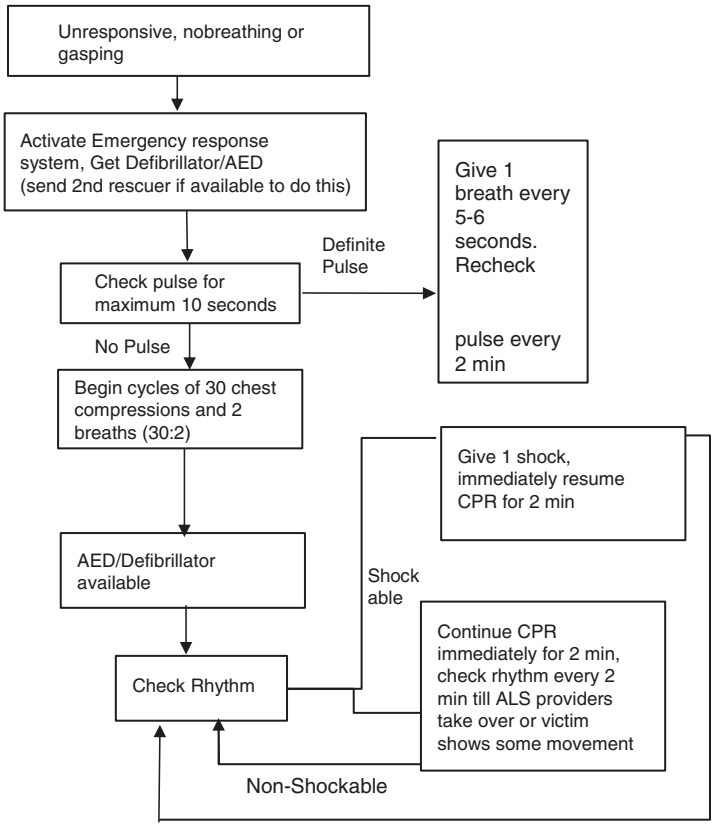

Fig. 1 Basic Life Support (BLS) Adult Algorithm
High-quality CPR: Rate of at least 100 compressions/min, compression depth of at least 2 inches (5 cm), allow chest recoil after each compression, minimize interruptions in chest compressions, avoid excess ventilation
Two or more rescuers should change compressor role every 2 min to prevent compressor fatigue and deterioration in quality and rate of chest compressions
Compressor role change should take less than 5 seconds
AED automated external defibrillator, Min minutes
Reference: American Heart Association, Basic Life Support Provider Manual 2016

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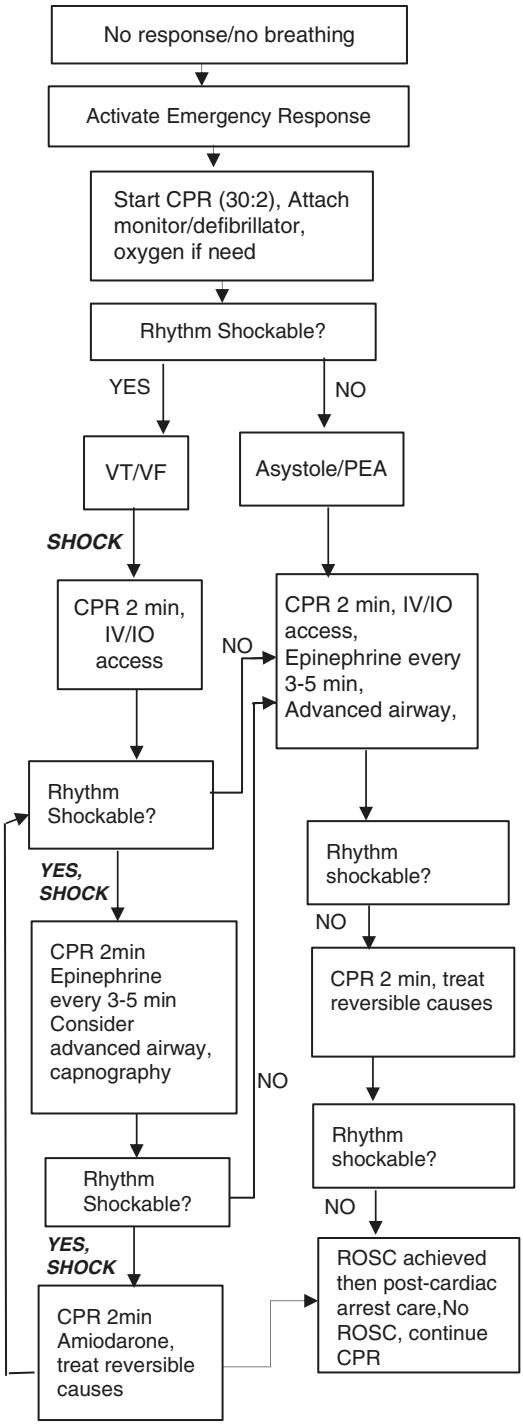

Fig. 2 Cardiac Arrest Adult Algorithm
Shock energy: Monophasic – 360 J, Biphasic – 120–200 J depending on manufacturer, if unknown – use highest dose available
Drugs: (1) Amiodarone IV/IO dose: first dose 300 mg bolus, second dose 150 mg. (2) Epinephrine IV/IO dose: 1 mg every 3–5 min. (3) Vasopressin IV/IO dose: 40 units (can replace first or second dose of epinephrine)
Capnography: If PETCO2 < 10 mmHg, improve CPR quality
ROSC criteria: Pulse and blood pressure present, sustained increase in PETCO2 (usually >40 mmHg), arterial pressure waves present with intra-arterial monitoring
Reversible causes of cardiac arrest: 5 Hs: hypovolemia, hypoxia, hydrogen ion (acidosis), hypo/hyperkalemia, hypothermia
5 Ts: tension pneumothorax, tamponade, cardiac, toxins, thrombosis, pulmonary, thrombosis, coronary
EA pulseless electrical activity, ROSC return of spontaneous circulation, PETCO2 end tidal carbon dioxide

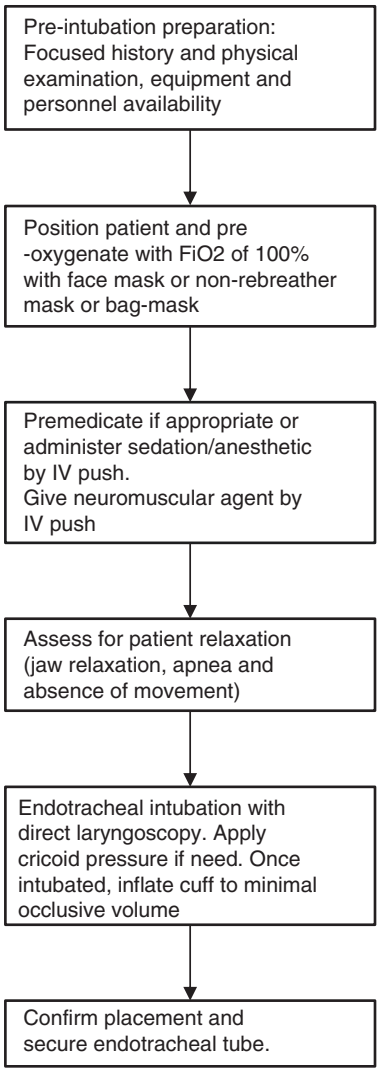

Fig. 3 Rapid sequence intubation (RSI)
If neck injury suspected, stabilize cervical spine; if no neck injury suspected, place in sniffing position
Drugs: Premedication: Atropine, glycopyrrolate, lidocaine. *Sedation/anesthetic agents:* Etomidate, fentanyl, ketamine, midazolam, propofol, thiopental. *Neuromuscular blocking agents:* Succinylcholine, vecuronium, cisatracurium, rocuronium
Confirm placement of endotracheal tube by: (a) direct visualization of ET passing through vocal cords. (b) Look for tube condensation and bilateral chest rise/fall with each ventilation. (c) 5-point auscultation. (d) End-tidal CO2 measurement by continuous waveform capnography or colorimetric CO2 detection. (e) Monitoring oxygen saturation (indirect evidence)
Choice of medication is based on user preference or availability
If multiple failed attempts of intubation, may consider placing surgical airway (cricothryroid-otomy, tracheostomy)
Reference: American Heart Association, Provider Manual 2016

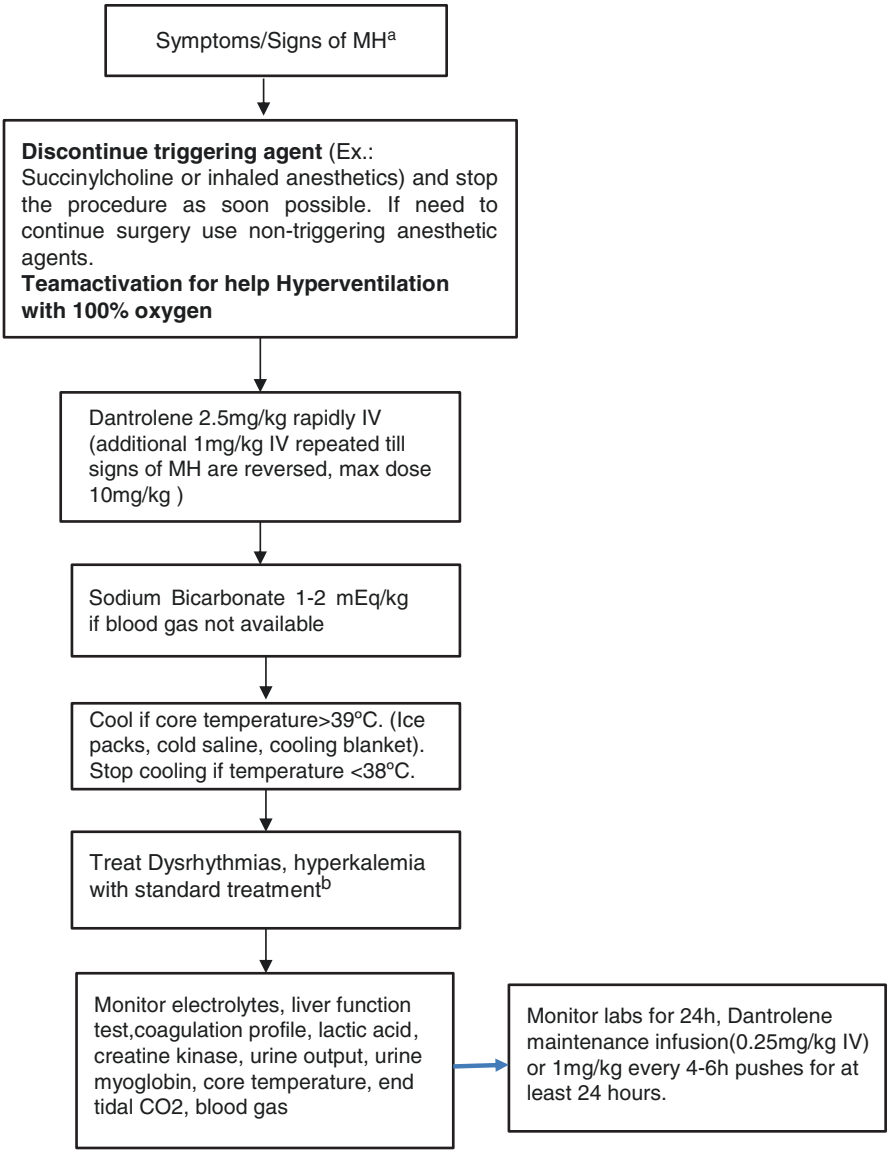

Fig. 4 Management of malignant hyperthermia
(a) *Symptoms/signs of MH:* Truncal/whole body rigidity, trismus, hyperthermia (late sign), tachypnea, tachycardia, masseter spasm (after succinylcholine), hyperhidrosis, acute kidney injury, metabolic acidosis, respiratory acidosis
(b) *Avoid CCB*: May cause hyperkalemia and trigger cardiac arrest in presence of dantrolene
Mneumonic – (*ABCDEF*) (A) Activation of team. (B) Bicarbonate. (C) Cooling. (D) Dantrolene. (E) Electrolyte correction. (F) Follow-up
CCB calcium channel blocker, MH malignant hyperthermia
Reference: Rosenberg H, Sambuggin N, Riazi S et al.; Malignant Hyperthermia Susceptibility Updated Jan 16, 2020

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